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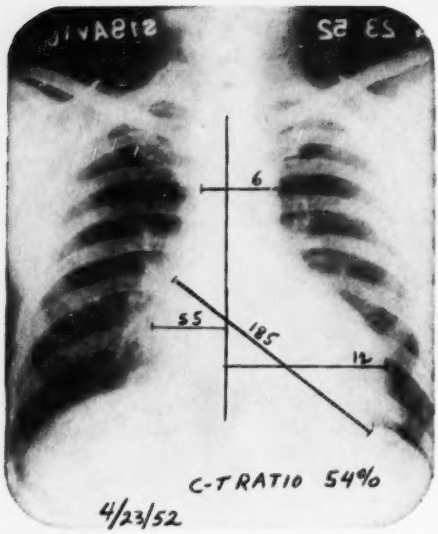
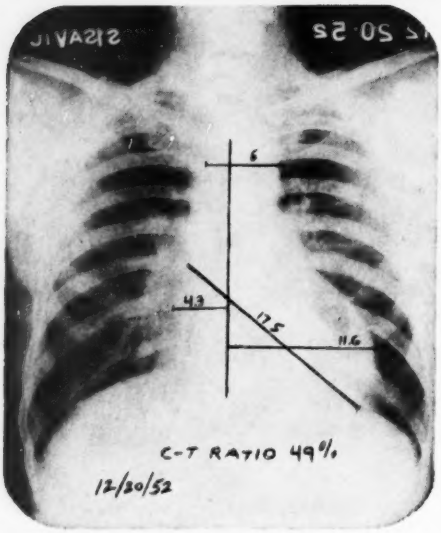


Patient F.S. before Methium: Cardio-thoracic ratio 54%, blood pressure 240/160 mm. Hg.[1]



After Methium: Cardio-thoracic ratio 49%, blood pressure 160/100 mm. Hg. This patient (F.S.) experienced no toxic side effects and did not lose a single day of work.[1]

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1. Kuhn, P. H.: Angiology 4:195 (June) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.
3. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.

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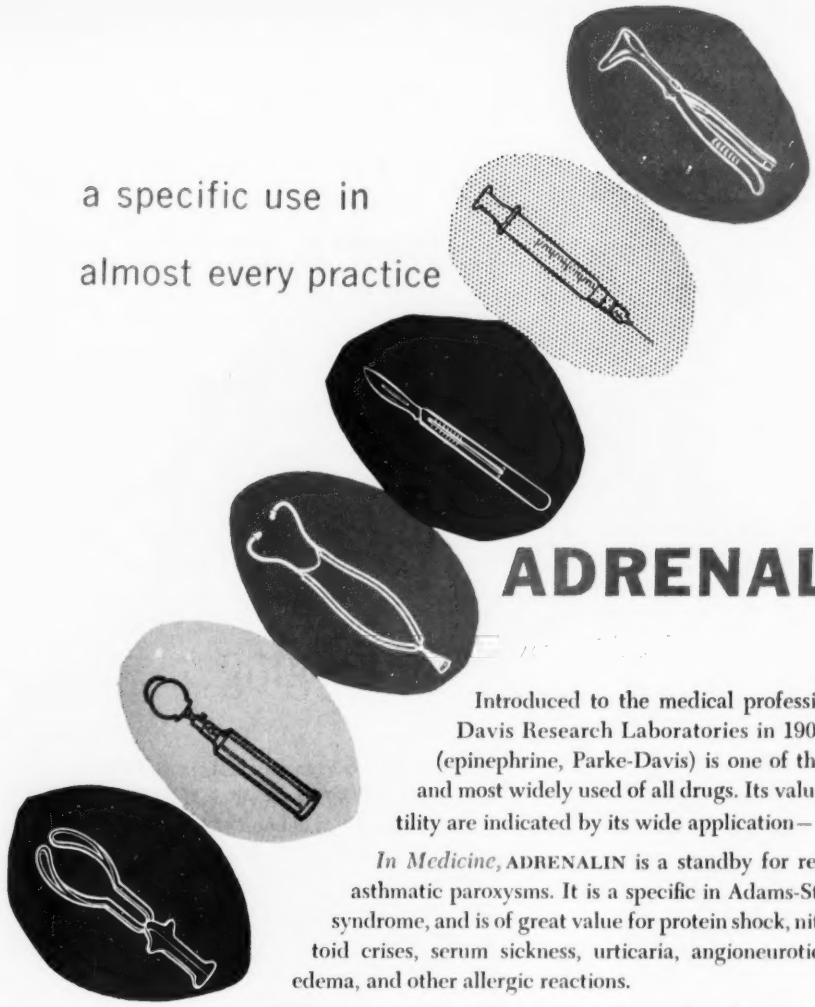

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*Stead, E. A., Jr., in Cecil, R. L., and Loeb, R. F.: Textbook of Medicine, ed. 8, Philadelphia, W. B. Saunders Co., 1951, p. 1065.

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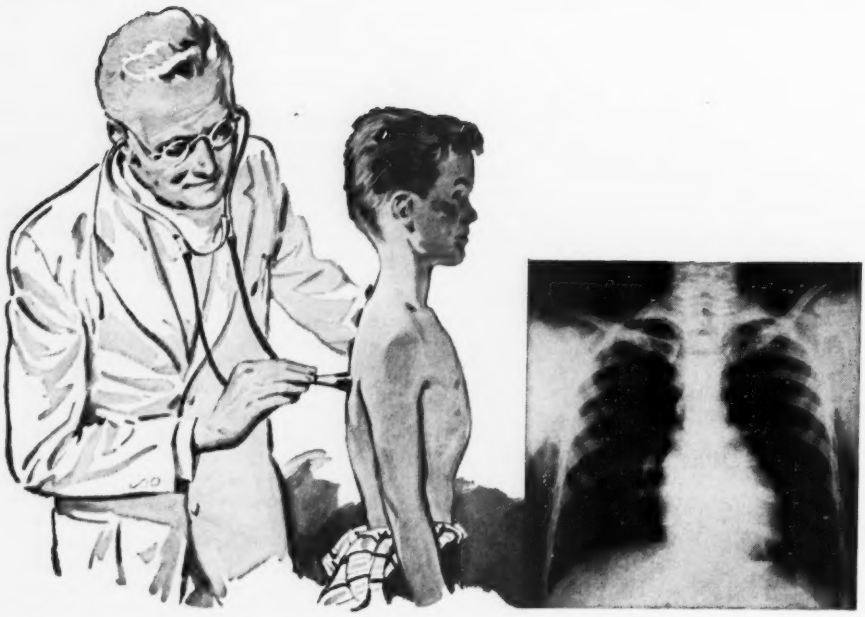

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PHRENIC OR POSTEMPHYSEMATOUS HYPERTENSION

CHARLES F. GESCHICKTER, M.D.
AND
ANTOINETTE POPOVICI, M.D.
WASHINGTON, D. C.

THE EXTENT of the concept of essential hypertension, after subtracting secondary forms related to increased cardiac output, increased intracranial pressure, and lesions of the adrenals or anomalies of the kidney, is largely determined by the standards chosen for the upper limits of normal blood pressure. Bell [1] states that blood pressure of 140/90 mm. Hg or higher occurs in about 50% of men and 60% of women over the age of 40. On the other hand, Master and co-workers [2] found in patients of 44 years of age and over an incidence of hypertension varying from 22 to 35%, taking as the upper limits of normal 150/100 mm. Hg. The consensus of statistics indicates that the incidence of hypertension in the general population is between 20 and 25%, if 95 mm. Hg for the diastolic pressure is taken as the dividing line between normal and abnormal. Recently Master and co-workers found the incidence of borderline hypertension (180/105 mm. Hg) to vary from 4 to 8% in men and 5 to 13% in women after the age of 44. If the above standards are accepted, in somewhere between 5 and 15% of the population significant hypertension develops after the end of middle life.

It is the purpose of this paper to call attention to the importance of pulmonary factors in such development of borderline hypertension after middle life and to the probable role of emphysema or pulmonary rigidity as one of the factors in essential hypertension. It is remarkable that in a recent symposium on the subject of high blood pressure there was not a single contribution in this field. In order to emphasize the point that we are not referring to hypertension of the pulmonic circulation as such, we have labeled this type of elevated blood pressure post-emphysematous or phrenic hypertension.

The importance of emphysema in hypertension was called to the attention of one of us (CFG) in the review of 285 cases of bronchial asthma, in which 25 of 60 patients over 40 years of age with both emphysema and chronic bronchial asthma had borderline or severe hypertension. That this elevation of blood pressure in chronic emphysema is not coincidental was confirmed by a maneuver in which

From the Department of Pathology, Georgetown University Medical Center.

This study was supported by a grant from the Geschickter Fund for Medical Research.

Read before the Section on Pathology and Physiology at the 102nd Annual Session of the American Medical Association, New York, June 2, 1953.

1. Bell, E. T.: Renal Diseases, Philadelphia, Lea & Febiger, 1946.

2. Master, A. M.; Garfield, C. L., and Walters, M. B.: Normal Blood Pressure and Hypertension, Philadelphia, Lea & Febiger, 1952.

further elevation of the diastolic pressure in these persons was accomplished by compression of the abdominal vena cava between the lumbar vertebrae and the posterior border of the liver, when the patient was put in recumbent lordosis. The fundamental concept advanced here, therefore, is that loss of negative intrathoracic pressure in emphysema results in increased venous pressure in the abdominal vena cava and in the renal veins. This in turn produces chronic congestion and stasis within the kidney, with compensatory arteriolar spasm, a characteristic feature of essential hypertension.

FREQUENCY OF EMPHYSEMA AND PULMONARY RIGIDITY IN THE LATTER YEARS

In the normal thorax the active muscular effort of inspiration is equaled by the elastic recoil of the pulmonic tissues aided by the recoil of the chest wall and diaphragm during expiration. In emphysema the lungs are progressively stretched beyond the capacity of normal recoil during expiration. The trapped expiratory air, which accumulates as increased residual air, aggravates the condition and makes pulmonary rigidity and emphysema a progressive process. Emphysema may be initiated by any factor impeding expiration, such as bronchial obstruction, thoracic or diaphragmatic fixation, or loss of elasticity within the pulmonary tissues themselves, in congestive heart failure or pulmonary fibrosis, but in the final analysis all forms of pulmonary emphysema are the result of impaired expiratory efficiency.

Loss of elasticity of intrinsic pulmonary tissue and loss of elasticity of the chest wall are part of the aging processes. Emphysema, therefore, constitutes a universal degenerative disease in the latter years of life, along with other similar conditions, such as arteriosclerosis, loss of elasticity of the superficial tissues, degenerative joint diseases, and involution of the sex organs. When one considers the universal effects of aging on the expansile property of the lungs and chest wall and also the frequency of diseases of the lung parenchyma, such as tuberculosis, bronchogenic carcinoma, atelectasis, pleural adhesions, postinfectious scarring, silicosis, asbestosis, and bronchial asthma, it is apparent that an exceedingly important and prevalent factor in hypertension will be established if emphysema can be causatively related to elevation of the arterial blood pressure.

RELATION OF EMPHYSEMA TO CIRCULATORY DISTURBANCES

We believe that the generally accepted statement that emphysema produces no circulatory complications until right-sided heart failure supervenes in advanced stages is erroneous. The work of Kountz and co-workers [3] in 1932 first indicated that the circulatory block in emphysema is not entirely within the pulmonary bed. It is also found in the great veins returning blood against positive intrapleural pressure. The statement also frequently made in texts that emphysema produces no change in arterial pressure is also open to question. In our opinion, both hypertension and myocardial infarction may be secondary to fully developed emphysema. We also subscribe to the view that left-sided cardiac hypertrophy may supervene as a direct consequence of mild chronic anoxia, which increases left ventricular output. This is the generally accepted explanation of the fact that when cardiac

3. Kountz, W. B.; Pearson, E. F., and Koenig, K. F.: Observations on Intrapleural Pressure and Its Influences on the Relative Circulation Rate in Emphysema, J. Clin. Invest. **11**:1281, 1932.

lesions attributable to the effects of emphysema are found they are characterized by enlargement of both ventricles rather than the involvement of the right chamber alone.[4]

In fully developed emphysema the progressive rigidity of the lungs, fixation of the chest wall, and retraction of the diaphragm lead to positive intrapleural pressure.[5] This increase in intrapleural pressure is associated with elevation of the venous pressure, which leads to renal congestion and a tendency to increased arterial pressure.

Altschule[6] in 1944 observed that the vital capacity is often somewhat low in patients with angina pectoris, apparently as a consequence of such noncardiac factors as emphysema and obesity. The frequent coexistence of emphysema and myocardial infarction, however, has not been sufficiently emphasized. In our patients with emphysema we were impressed with the frequency of bundle branch block and other myocardial lesions. In this connection it should be pointed out that the coronary venous return is directly to the right auricle. The pressure in this chamber is identical with the intrathoracic pressure and in emphysema, therefore, tends to be elevated. This impediment to coronary outflow we believe is a factor in the increased incidence of myocardial infarction in advanced emphysema, when it is complicated by coronary atherosclerosis and asthmatic attacks, which further elevate intrathoracic pressure. These asthmatic attacks can precipitate myocardial infarction in such cases. It seems incredible to a pathologist that venous obstruction, as well as arterial occlusion, has not been heretofore emphasized as a cause of myocardial infarction.

CLINICAL OBSERVATIONS

In a series of 75 patients over 40 years of age with bronchial asthma and a history of asthmatic attacks of two or more years' duration, 60 patients (80%) had emphysema. Of the 60 patients with postasthmatic emphysema 28, or 46%, had some degree of arterial hypertension. This is particularly significant, since with the use of similar standards the corresponding percentage of hypertension is only 20 to 25% in the general population. These standards are 160/90 mm. Hg for the upper limits of normal blood pressure. The majority of the patients in our series were 51 to 65 years of age, averaging 56 years, and the majority had asthmatic attacks from 4 to 15 years. In those patients under 45 years of age with emphysema and circulatory complications, the asthmatic attacks had occurred for 10 or more years (Fig. 1). On the other hand, if the patients were over 45 years of age, with shorter histories of asthmatic attacks, there was frequently a complicating history of pneumonitis or some other cause of pulmonary fibrosis. It is important to realize that in patients over 45 years of age with bronchial asthma emphysema, pulmonary fibrosis, and circulatory complications are interrelated phenomena (Fig. 2; Tables 1 and 2).

4. Kountz, W. B.; Alexander, H. L., and Dowell, D.: Emphysema Simulating Cardiac Decompensation, J. A. M. A. **93**:1369, 1929.

5. Christie, R. V.: The Elastic Properties of the Emphysematous Lung and Their Clinical Significance, J. Clin. Invest. **13**:295, 1934.

6. Altschule, M. D.: Cardiovascular Dynamics in Patients with Angina Pectoris, Am. Heart J. **27**:322, 1944.

The occurrence of pulmonary fibrosis as a consequence of attacks of pneumonitis, healed tuberculosis, or silicosis tends to aggravate pulmonary rigidity, a predisposing factor in phrenic hypertension. On the other hand, the increased positive intrathoracic pressure in these cases, by impeding coronary venous outflow to the

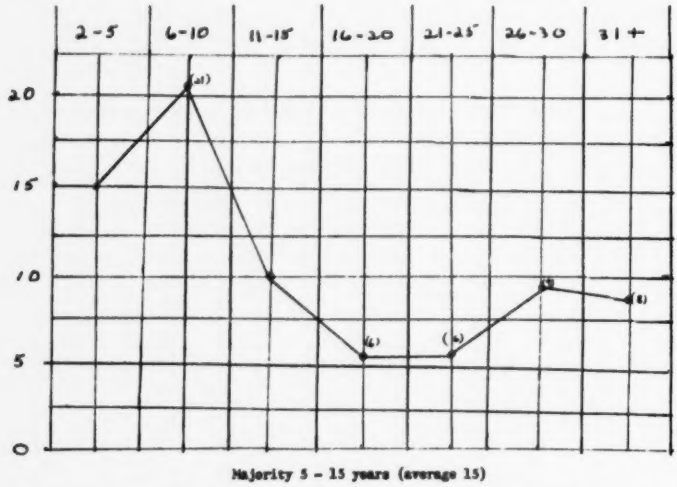

Fig. 1.—Duration of bronchial asthma in 60 patients over age 40 with emphysema.

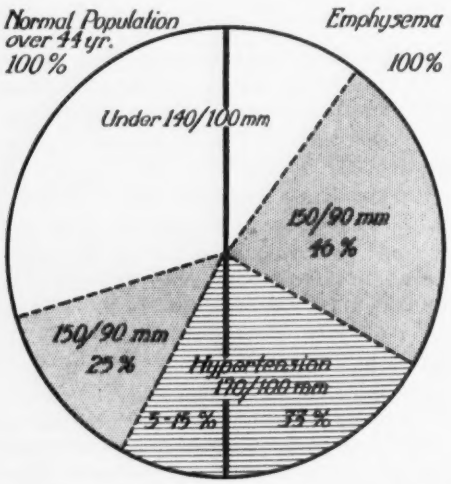

Fig. 2.—Incidence of hypertension in patients with emphysema compared to the incidence in the general population.

right auricle, increases the incidence of myocardial infarction. If the myocardial damage is severe, it tends to counteract the development of hypertension or to lower a preceding elevated blood pressure. It is significant, therefore, that 18 of the 60 patients with emphysema had varying degrees of myocardial damage.

TABLE 1.—*Asthma and Emphysema with Hypertension*

Patient	Age, Yr.	Duration, Yr.	Etiology	B. P.	Complications
1	57	27	Colds and weather	190/100 195/120	Emphysema Gr. III, pneumonitis, dorsal kyphosis
2	65	3	Cold, rhinitis	170/90 175/95	Emphysema Gr. II, bronchitis
3	61	28	Colds, sinusitis	170/100 180/90	Emphysema Gr. II, cardiac decompensation; circulation time 30 sec.
4	46	2	6 attacks pneumonitis	145/90 170/120	Emphysema Gr. II, fixed diaphragm, myocarditis, pulmonary fibrosis
5	59	32	6 attacks pneumonia	175/96	Emphysema Gr. II, anginoid attacks
6	60	10	Bronchitis, colds	170/86 175/90	Emphysema Gr. I, obesity, circulation time 18 sec., Qrs notching
7	78	8	Colds, bronchitis	180/110	Emphysema Gr. II, cardiac decompensation
8	41	37	Pollens, colds	150/110 160/110	Emphysema Gr. IV, asthmatic bronchitis
9	57	8	Colds	160/110	Emphysema Gr. II, myocarditis, kyphosis
10	78	15	Pollens, colds	170/70 180/85	Emphysema Gr. II, cardiac decompensation
11	48	10	Cereals, dusts, sinusitis	170/110 175/115	Emphysema Gr. II
12	63	15	Pollens, colds	170/90 180/90	Emphysema Gr. II, heart block
13	63	30	Colds	160/90 176/106	Emphysema Gr. II, dorsal kyphosis, osteoarthritis
14	60	22	Colds	150/100 160/105	Emphysema Gr. II, heart block
15	62	8	Pollens, colds	175/90 190/110	Emphysema Gr. I
16	44	12, as child	Pollens	190/110	Emphysema Gr. III, dorsal kyphosis, cardiac enlargement
17	67	35	Pollens, colds	200/90 210/95	Emphysema Gr. IV, myocardial damage
18	67	25	Pollens, colds	165/110 165/110	Emphysema Gr. III, dorsal kyphosis, myocardial infarction
19	65	4	Pneumonia, heart trouble	180/110	Emphysema Gr. III, circulation time 29 sec., myocardial damage
20	64	4	Colds, sinusitis	210/80 220/95	Emphysema Gr. II, obesity
21	60	2	Berylliosis	180/100	Emphysema Gr. III, pulmonary fibrosis
22	64	30	Colds, bronchitis	160/110	Emphysema Gr. IV, myocardial damage
23	64	3	Colds	180/90 185/100	Emphysema Gr. II, myocarditis
24	62	2	Colds	190/110	Emphysema Gr. II
25	56	15	Pollens, colds	165/95	Emphysema Gr. I
26	60	3	Grease, smoke	165/100	Emphysema Gr. I, vital capacity 2.6
27*	48	8	Pollens	150/85 200/110	Emphysema Gr. I
28	64	4	Pneumonia (2 times)	165/95	Emphysema Gr. III, cardiac

* Two-year interval between readings.

TABLE 2.—*Asthma and Emphysema Without Hypertension*

Patient	Age, Yr.	Duration, Yr.	Etiology	B. P.	Complications
1	60	30	Colds, weather	160/90	Emphysema Gr. III
2	47	10	Pollens	150/90	Emphysema Gr. I
3	56	8	Pneumonia (2 times)	140/80	Emphysema Gr. I
4	58	40	Pollens, dusts	164/86	Emphysema Gr. I
5	55	24	Oils in food, colds	166/76	Emphysema Gr. I
6	58	10	Pneumonia (2 times)	140/85	Emphysema Gr. I
7	42	34	Pollens, sinusitis, colds	114/68	Emphysema Gr. II
8	54	8	Pollens	150/85	Emphysema Gr. I
9	47	10	Pneumonia (3 times) colds	130/80	Emphysema Gr. II
10	66	5	Colds, weather	130/70	Emphysema Gr. I
11	64	10	Sensitive to acetylsalicylic acid, colds	140/90	Emphysema Gr. II, heart block
12	56	2	Colds, healed tuberculosis	155/90	Emphysema Gr. I
13	47	9	Ragweed, colds	145/85	Emphysema Gr. I, vital capacity 1.8
14	45	25	Ragweed, colds	150/85	Emphysema Gr. II, cardiac, circulation time 26 sec.
15	56	20	Smoke, colds, weather	120/90	Emphysema Gr. I
16	53	14	Pollens	145/85	Emphysema Gr. I
17	49	8	Pollens, colds	150/90	Emphysema Gr. I
18	57	9	Colds, weather	110/85	Emphysema Gr. II
19	70	20	Pollens	140/80	Emphysema Gr. I
20	49	15	Ragweed, sinusitis	136/68	Emphysema Gr. III
21	56	4	Oils veg., colds	110/70	Emphysema Gr. II, bronchitis, circulation time 24 sec.
22	44	10	Weather, food, sinusitis	140/100	Emphysema Gr. II
23	65	30	Pollens, colds	145/68	Emphysema Gr. II
24	62	17	Colds, pollens	118/68	Emphysema Gr. III, cardiac, bronchitis
25	62	60	Pollens, paints	140/90	Emphysema Gr. II
26	65	4	Colds, pollen	110/70	Emphysema Gr. II, cardiac
27	45	2	Colds	145/90	Emphysema Gr. II
28	70	30	Colds	165/90	Emphysema Gr. II, cardiac
29	32	10	Colds	160/90	Emphysema Gr. II, dorsal kyphosis
30	62	5	Colds, bronchitis	150/80	Emphysema Gr. I, myocarditis
31	52	25	Pollens	130/90	Emphysema Gr. II
32	69	10	Silicosis, bronchitis	140/80	Emphysema Gr. II, pulmonary fibrosis

The blood pressure readings for these patients were not made until a week or more after ephedrine or epinephrine therapy had been withdrawn. As will be reported elsewhere, all our patients were treated with quinoline derivatives with or without supplementary doses of aminophyllin. Blood pressure was not measured during an acute attack of bronchial asthma.

As Meakins [7] has stated, transient hypertension and bronchial asthmatic attacks are frequently associated. On the other hand, mild degrees of status asthmaticus along with emphysema in patients who are ambulatory is a definite factor in

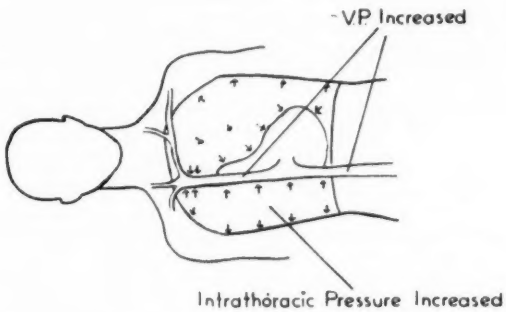

Fig. 3.—Increase in venous pressure with increased intrathoracic pressure (after Burch, G. E.: Primer of Venous Pressure, Philadelphia, Lea & Febiger, 1950).

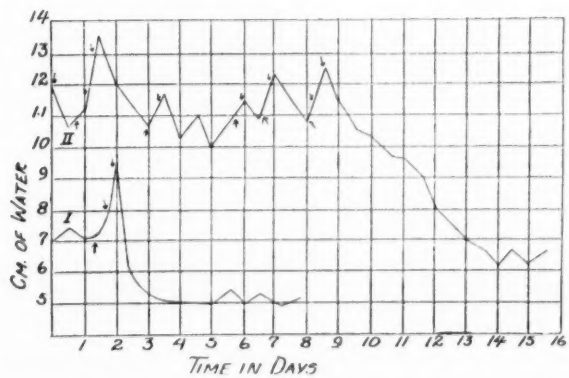

Fig. 4.—Increase in venous pressure with asthmatic attacks (After Kountz and co-workers [3]). Record of a person with asthma who had only a mild degree of emphysema. The venous pressure immediately dropped to normal after an asthmatic attack. Arrow up indicates onset of attack. Arrow down indicates an injection of epinephrine.

elevating blood pressure to hypertensive levels. In some cases the blood pressure, after being at hypertensive levels for months, may fall to normal limits when the asthma is successfully controlled and the patient is put on partial bed rest, with restricted activity. When, however, severe thoracic deformity has supervened, the hypertension persists even though the asthmatic attacks have ceased and have not occurred for a period of 5 to 15 years. The significant feature is that the degree

7. Meakins, J. C.: Cardiac Asthma, Postgrad. Med. **13**:89, 1953.

of emphysema and positive intrathoracic pressure determines the degree of elevation of the venous pressure. The resultant venous congestion determines the arterial hypertensive level regardless of whether or not the asthmatic attacks are present (Figs. 3 and 4; Table 3). However, recurrent asthmatic attacks tend to elevate the blood pressure paroxysmally above the hypertensive base line. We have observed the development of hypertension with emphysema and fixation of the chest wall, secondary to spondylitis, in patients in whom there was no history of bronchial asthma.

REPORT OF CASES

In the following two cases of asthma with emphysema the patients did not have hypertension when first observed but developed it subsequently.

TABLE 3.—*Intrapleural and Venous Pressures in Normal Persons and Emphysematous Patients**

Patient	Vital Capacity, Cc.	Tidal Air, Cc.	Intrapleural Pressure,† Tital Air: Inspiration, Cm. Water	Intrapleural Pressure,† Tital Air: Expiration, Cm. Water	Intrapleural Pressure, Tidal Air, 500 Cc.: Inspiration, Cm. Water	Intrapleural Pressure, Tidal Air, 500 Cc.: Expiration, Cm. Water	Intrapleural Pressure, Valsalva Experiment, Cm. Water	Venous Pressure, Cm. Water	Venous Pressure at End of During Asthmatic Attack, Cm. Water	Venous Pressure at End of Valsalva Experiment, Cm. Water
1. Normal	3,800	375	—4	—6	—5	—7	+6	4.5	..	18
2. Normal	4,200	425	—3	—7	—3	—9	+8	5	..	16
3. Normal	4,500	480	—4	—8	—4	—8	+10	5	..	18
4. Emphysema	4,100	380	—2	—5	...	...	+12	6	10	14
5. Emphysema, asthmatic attack	2,200	200	+2	—8	...	...	....	...	10	12
6. Emphysema, asthmatic attack	1,900	300	+4	—3	...	...	....	...	14	14
7. Emphysema	3,200	225	—1	—6	—3	—9	....	6.5	7	..
8. Emphysema	2,700	300	—2	—4	—2	—6	....	6	..	..
9. Emphysema	2,800	270	—1	—4	...	...	....	...	..	..
10. Emphysema (primary pulmonary arterial sclerosis)	1,700	200	+2	—8	...	...	....	14	..	..

* Adapted from Kountz and co-workers.[8]
† All intrapleural pressures taken in midaxillary line in fifth interspace.

A man of 41 was first seen in January 1949. He gave a history of asthma and hay fever since the age of 4 years and had had recurrent attacks of wheezing and cough for the past several years, with colds. Prior to that time he had been relatively free from asthma since the age of 21.

At the time of examination, 1949, there were inspiratory and expiratory rales over the entire chest. The outstanding feature was a Grade IV emphysema. His blood pressure at this time was normal, 130/90.

Three and one-half years after the initial examination he was seen again for asthmatic attacks, June 10, 1952. At this time his blood pressure readings on several examinations varied from 150/110 to 156/113. When he was in the position of recumbent lordosis the blood pressure varied from 150/110 to 160/113. The returning control pressure after he had been lying down for 20 minutes was 148/110.

The second patient was a woman of 48 who had asthma for eight years, which was worse in the spring and in the fall pollen season. The asthma was preceded by hay fever. Exertion and breathing cold air precipitated asthma. Examination Jan. 28, 1950, showed expiratory rales at both lung bases, a Grade II emphysema, and a blood pressure of 150/85. The patient was free of asthma for a year and eight months. She then returned with renewed attacks of wheezing and anginoid pains in the chest. She also complained of headaches. When she was examined Aug. 26, 1952, the blood pressure was 200/110. The controlled blood pressure after she lay down was 190/110, and when she took the position of lumbar lordosis the blood pressure rose to 200/120. The electrocardiogram showed left ventricular preponderance, which was not present on the initial reading.

The following two patients had rheumatoid spondylitis and normal blood pressure when first seen. Subsequently mild degrees of hypertension developed.

A man of 56, first seen Nov. 27, 1948, had had spondylitis with ankylosis of the spine since 1945. On examination the findings were entirely related to his arthritis. There was limited expansion of the chest, with rigidity of the spine extending from the midthoracic vertebrae to the cervical vertebrae. The blood pressure was 142/90. This patient was reexamined in July 1952, nearly four years later and six years after the onset of arthritic symptoms. The only added symptom was occasional dizziness. The blood pressure readings at this time ranged from 160/100 to 180/115. When the lumbar lordosis maneuver was done, his blood pressure after reclining for 30 minutes was 160/104; with recumbent lumbar lordosis it rose to 180/120 and then returned to the previous reading of 160/104 when he was again placed in simple recumbent position.

A man aged 39 was first seen Jan. 10, 1948. He had had rheumatic involvement of the spine for the past four years, and roentgenographic examination revealed complete ossification of paravertebral ligaments. There was limitation of respiratory movements in the chest; the blood

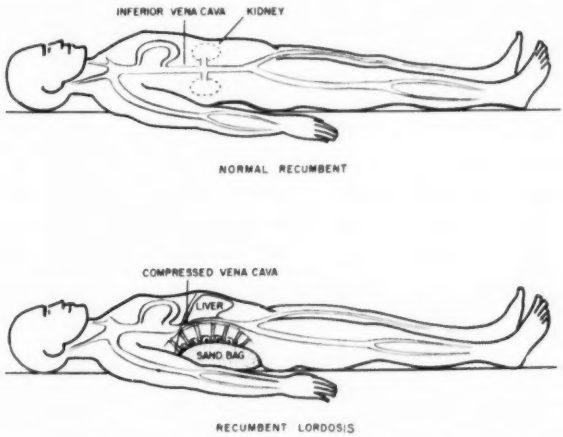

Fig. 5.—The recumbent lordosis test. The lower figure illustrates the compression of the inferior vena cava between the lumbar spine and the posterior surface of the liver when the patient is in the lordotic position (lumbar spine hyperextended over a sandbag).

pressure was 120/70. He was seen again April 28, 1953, elsewhere, at which time there was recurrent rheumatoid spondylitis, restricted pulmonary ventilation due to fixed thoracic cage, and a blood pressure of 190/115.

THE RECUMBENT LORDOSIS TEST

It occurred to one of us (CFG) that since the elevated arterial pressure observed in chronic pulmonary emphysema might result from renal congestion secondary to increased pressure in the vena cava (the latter in turn produced by increased intrathoracic pressure) a clinical demonstration of this sequence could be achieved. The emphysematous patient was, therefore, placed on his back on the examining table and a sand bag was inserted under the lumbar spine to achieve a position of recumbent lordosis, with head tilting backward on the table (Fig. 5). In this position the inferior vena cava is compressed between the lumbar spine and the posterior-inferior edge of the liver. After this maneuver blood pressure readings are made at minute intervals for five minutes and then the normal recumbent position is resumed and a final return pressure taken at the end of another five minutes. In normal persons the blood pressure is not elevated, as a rule. Instead the compression of the venous return to the heart may bring about in some persons

diminished cardiac output, with fall in both systolic and diastolic pressure (Table 4). On the other hand, in borderline hypertension and hypertension with emphysema or fixation of the thoracic cage there is, in a matter of two to five minutes, an elevation of 10 to 20 points in the diastolic pressure. A rise of 15 mm. or more in

TABLE 4.—*Recumbent Lordosis Test-Controls*

Patient	Sex	Age, Yr.	Diagnosis	Control Pressure	Lordosis Pressure	Return Pressure
1	M	7	Normal	100/70	110/80 105/75	100/60
2	F	8	Normal	100/70	90/68 90/60	100/70
3	M	10½	Normal	110/70	108/60 105/60	105/70
4	M	10½	Normal	110/68	110/58 110/60	110/60
5	M	41	Normal	120/64	105/60 102/65	102/65
6	F	47	Normal	110/70	108/70 105/68	110/70
7	M	48	Normal	112/63	112/63 108/62	112/65
8	F	55	Normal	140/90	138/83 140/82	145/90
9	M	55	Normal	105/70	105/70 108/75	105/70
10	F	48	Normal	150/90	150/88 150/90	148/90
11	F	52	Normal	160/90	150/95 150/90	160/90
12	F	49	Normal	140/90	130/88 130/86	130/90
13	M	51	Normal	136/82	124/94 134/100	136/88
14	M	38	Normal	135/78	120/80 125/75	130/80
15	F	60	Osteoarthritis	140/92	130/96 125/88	125/88
16	F	48	Hodgkin's disease	130/86	140/70 130/90 130/86	134/88
17	F	36	Lupus erythematosis	120/80	124/84 118/76	120/80
18	M	65	Normal	150/88	138/75 130/78	140/82
19	F	53	Mammary adenosis	124/74	120/90 130/90	124/74
20	F	25	Pregnant 4½ mo.	125/68	130/75 130/75	125/68
21	F	40	Obesity	148/100	160/80 165/90	150/90
22	F	60	Avitaminosis	136/74	150/90 146/90	144/88
23	F	48	Obesity	165/90	156/100 150/105	150/90
24	F	45	Obesity	150/94	148/98 140/100	140/94
25	F	67	Arthralgia	170/90	175/98 170/95	170/90

the diastolic pressure is considered a positive test. The systolic pressure may rise but usually drops back within three to five minutes to a less marked elevation, of from 5 to 10 mm. (Tables 5 and 6).

It is interesting that somewhat similar observations were reported in 1943 by Talbot and co-workers.[8] In studying the blood pressure responses of hypertensive patients in varying positions these authors noted that the diastolic level rose

8. Talbot, J. H.; Castleman, B.; Smithwick, R. H.; Melville, R. S., and Pecora, I. J.: Renal Biopsy Studies Correlated with Renal Clearance Observations in Hypertensive Patients Treated by Radical Sympathectomy, J. Clin. Invest. **22**:387, 1943.

TABLE 5.—*Recumbent Lordosis Test—Emphysema with Hypertension*

Patient	Sex	Age, Yr.	Diagnosis	Control Pressure	Lordosis Pressure	Return Pressure
1	F	37	Asthma, emphysema	140/90	150/95 150/100	140/90
2	M	44	Asthma, emphysema, kyphosis	190/104	240/115 240/120	190/110
3	M	62	Asthma, emphysema, myocarditis	145/75	150/90 120/90	130/90
4	F	63	Asthma, emphysema, myocarditis	170/90	160/96 168/95	170/90
5	M	48	Asthma, emphysema	170/120	165/140 175/160	168/128
6	M	57	Asthma, emphysema, myocarditis	160/100	180/100 174/104	156/94
7	M	41	Asthma, emphysema	150/110	160/112 160/110	148/110
8	F	55	Emphysema	190/118	200/138 200/138	190/118
9	F	46	Asthma, emphysema	165/95	190/118 190/125	170/88
10	M	52	Asthma, emphysema	130/90	145/105 140/105	130/90
11	F	62	Asthma, emphysema	205/105	192/120 210/120	208/100
12	F	46	Asthma, emphysema	200/100	205/120 205/115	190/110 215/120 (standing)
13	M	57	Asthma, emphysema, myocarditis	130/80	150/105 140/105	130/86
14	M	60	Emphysema, pulmonary fibrosis	170/90	190/105 185/110	160/90
15	M	62	Asthma, emphysema, myocarditis	160/90	160/100 160/108	160/90
16	F	67	Asthma, emphysema, myocarditis	180/110	170/130 180/140	164/90
17	F	48	Asthma, emphysema	190/110	200/120 190/120	190/110
18	M	63	Emphysema, myocarditis	140/85	170/110 160/90	140/85
19	F	67	Emphysema	200/94	260/120 220/122	205/110
20	M	63	Emphysema, obesity	145/80	175/110 180/115	150/90
21	M	50	Emphysema, obesity, lordosis	170/90	170/98 160/98	170/90 180/110 (standing)
22	M	59	Asthma, emphysema Gr. I	160/98	155/110 180/110	160/98

TABLE 6.—*Recumbent Lordosis Test—Osteoarthritis or Spondylitis with Hypertension*
Recumbent Lordosis Test

Patient	Sex	Age, Yr.	Diagnosis	Control Pressure	Lordosis Pressure	Return Pressure
1	F	59	Osteoarthritis	170/90	185/105 160/115	170/90
2	F	47	Obesity, lordosis	140/90	160/105 150/108	130/70
3	M	44	Obesity	210/130	230/130 210/140	210/130
4	F	52	Osteoarthritis	228/120	196/120 216/124	212/120
5	F	58	Osteoarthritis	150/70	186/90 196/100	160/80
6	F	47	Osteoarthritis	130/85	160/110 165/110	130/85
7	F	61	Osteoarthritis	190/119	190/120 160/110	170/110
8	F	70	Osteoarthritis	210/130	220/135 215/135	210/130
9	F	58	Obesity	250/108	250/120 240/130	250/108
10	F	52	Osteoarthritis	160/90	180/112 180/110	160/90
11	F	54	Osteoarthritis	158/90	180/100 155/110	165/90
12	F	55	Osteoarthritis	180/100	200/100 215/120	184/108
13	M	56	Spondylitis	166/104	170/118 180/120	160/110
14	M	70	Spondylitis	160/110	230/130 175/130	170/110

abnormally when the patients were shifted from the recumbent to the upright position. This shift was recorded by taking five readings of the blood pressure at one-minute intervals when the patient was lying down and then repeating the procedure when the patient was standing. An average rise of 20 mm. or more in the upright position was considered abnormal. Renal blood flow studies were performed in a single case, in which the patient in the horizontal position was first subjected to one minute of immersing the hand in cold water and then, 30 minutes later, was shifted from the recumbent to the vertical position for five minutes. In this patient the renal plasma flow decreased from 400 to 250 cc. per minute on immersing the hand in ice water and the renal plasma flow remained reduced for 30 minutes, at which time the patient was tilted to the vertical position for five minutes, when the renal plasma flow decreased still further to 100 cc. per minute and then in the following 20 minutes returned to the starting pressure. These

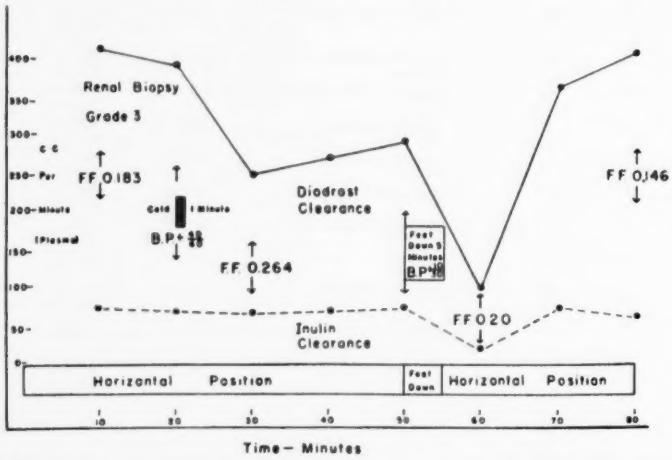

Fig. 6.—The effect of immersing the hand in cold water and of tilting into the upright position upon blood pressure and renal blood flow in a hypertensive patient (after Talbot and co-workers [8]).

authors concluded that factors which influence the visceral blood flow may be of fundamental importance in hypertension by influencing the renal state of ischemia (Fig. 6).

Bull [9] reviewed the literature on postural proteinuria and found that renal function remained essentially unchanged when the patient was shifted from the recumbent to the erect posture. It was also not unusually influenced when the patient was in recumbent lordosis. However, in the erect lordotic position, in which both the factors of lordosis and gravity were working simultaneously, the renal plasma flow fell 33 to 80% of the figure observed in recumbent lordosis. The filtration rate was reduced 50 to 95%, and the urine flow was markedly reduced. This author concluded that in the erect lordotic position and, to a lesser extent, in the recumbent lordotic position, the inferior vena cava is compressed against the spine by the posterior surface of the liver, which produces increased renal venous pressure and passive renal congestion.

9. Bull, G. M.: Postural Proteinuria, Clin. Sc. **7**:77, 1948.

The important point of these observations is that in normotensive persons neither the recumbent lordotic position nor the upright position alone is sufficient to alter renal function significantly but that a combination of both is required.[10] On the other hand, we have demonstrated that the recumbent lordotic position alone is sufficient to influence blood pressure, probably through renal congestion, in patients with borderline hypertension with emphysema, and Talbot has shown that the upright position alone will elevate blood pressure and alter renal function in certain persons with hypertension. It can be concluded, therefore, that either recumbent lordosis or upright position will affect renal physiology in certain persons with hypertension, whereas a combination of both lordosis and upright position is necessary to affect renal physiology in normal persons.

That upright lordosis which produces persistent orthostatic albuminuria may be a factor in producing hypertension in later years is indicated by the studies of Christierin and his co-workers.[11] They followed 4,387 cases of benign albuminuria for periods of several to 30 years (average 7 years). There were 99 deaths; 7 were from nephritis and 8 from tuberculosis. In the remaining cases there was an unusually high percentage of deaths from hypertensive cardiovascular disease.

TABLE 7.—*Recumbent Lordosis Test*

	Controls	Emphysema with Hypertension	Osteoarthritis with Hypertension
Cases, total no.	25	22	14
Control pressure	100/70-140/92	140/90-205/118	140/90-220/120
Lordotic pressure reduced, no.	16	0	0
Lordotic pressure elevated 0 to +10 mm., no.	9	7	7
Lordotic pressure elevated 15 mm. or more, no.	0	15	10

With the recumbent lordosis test it can be demonstrated in normal persons (Table 7) that the blood pressure either remains essentially stationary or falls. On the other hand, in patients with borderline or fully developed hypertension both the systolic and the diastolic blood pressure rises, the diastolic ordinarily increasing 15 mm. or more. The elevation in systolic pressure is less significant, since it is influenced by the discomfort of the position. It may actually fall. This recumbent lordosis maneuver throws an important light on the relation of obesity to many cases of hypertension. Patients with emphysema and obesity when put in the upright position show an increase in blood pressure that is over and above that in the recumbent lordotic position. Examination of their stance indicates that in addition to the emphysema two additional factors are involved (Figs. 7 and 8). The influence of gravity further increases the venous pressure and congestion of the kidneys. In addition to this, these overweight patients usually assume a position of lordosis, with protruding abdomen, which further obstructs the venous return to the thorax. This double effect on standing explains in part the beneficial effects on blood pressure observed with weight reduction or bed rest. It is common experience that loss of weight (with correction of posture) lowers blood pressure. The postural correction which occurs with weight reduction heretofore has not been emphasized.

10. We have found that the lumbar lordosis test may be positive in the last trimester of pregnancy.

11. Christierin, C. L.; Dublin, L. I., and Marks, H. H.: Studies in Albuminuria, Proc. M. Directors A. Life Ins. America **26**:160, 1940.

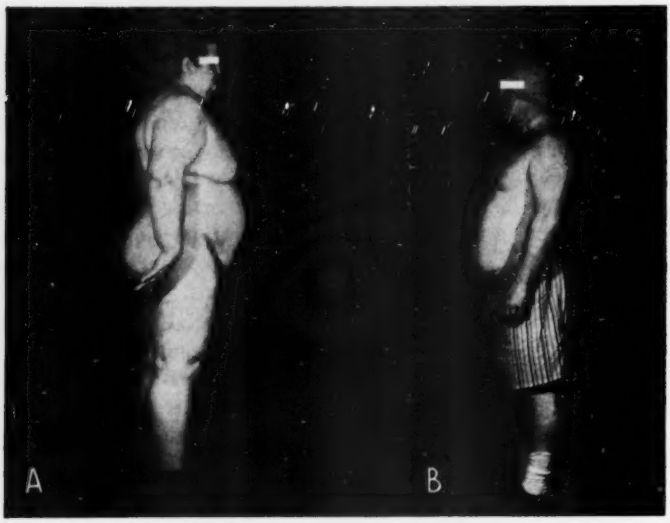

Fig. 7.—Orthostatic elevation of venous pressure in patients with hypertension. *A*, obesity and lordosis in a patient with a blood pressure of 245/130. *B*, lordosis with "pot belly" in a patient with a blood pressure of 180/110. (Each of these patients had a positive recumbent lordosis test.)

Fig. 8.—Roentgenogram of a patient with postasthmatic emphysema and a blood pressure of 220/110, showing dorsal kyphosis and lumbar lordosis (positive recumbent lordosis test).

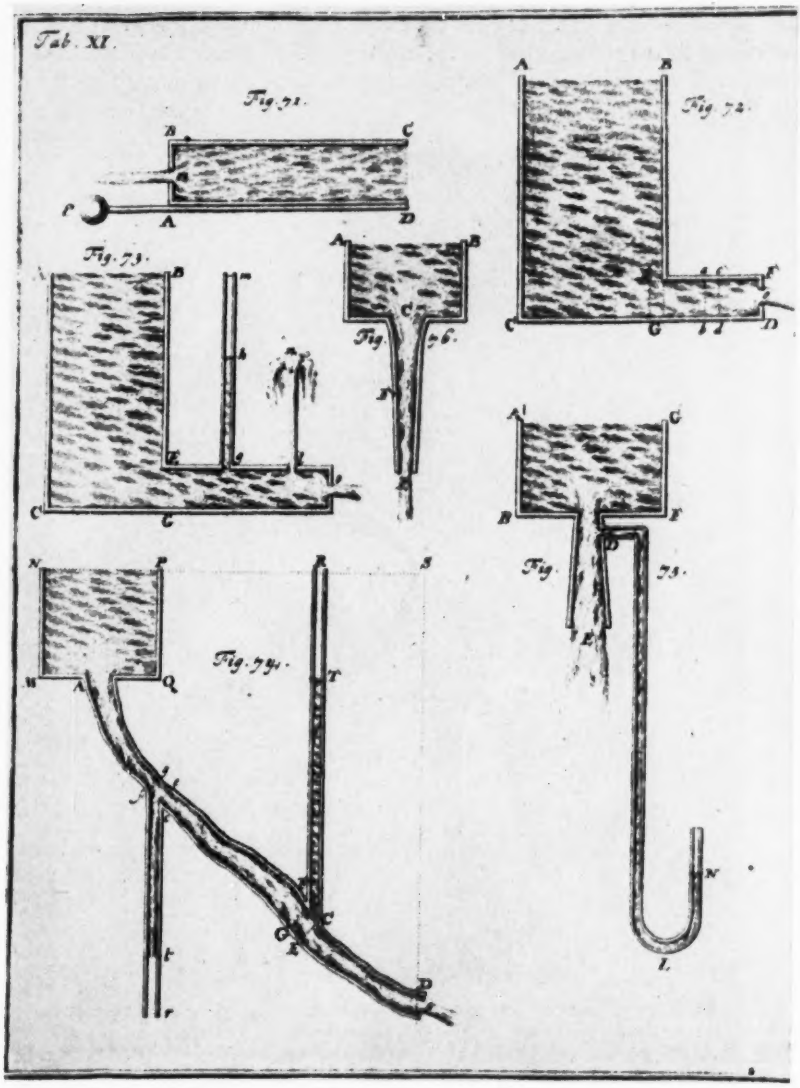

Fig. 9.—Original illustrations from Bernoulli [12] published in 1738, demonstrating that fluid pressure is inversely proportional to velocity.

CORRECTION OF HYPERTENSION BY PORTOCAVAL SHUNT

According to our concept of phrenic hypertension, the primary effect is a reduction in the velocity of the venous return via the inferior vena cava to the right heart. In accordance with Bernoulli's principle,[12] the venous pressure is inversely proportional to the velocity, and as the velocity falls in the inferior vena cava the pressure will rise in the renal veins which join the mainstream at right angles (Fig. 9).

Fig. 10.—Viscera obtained at autopsy from a hypertensive dog with Page-wrapped kidneys. The blood pressure was successfully lowered for 22 months by a portocaval shunt. *S*, shunt; *VC*, inferior vena cava; *PV*, portal vein; *K*, *K'*, wrapped kidneys.

Kountz and co-workers,[3] studying experimental emphysema in dogs, found that as the lungs became larger intrapleural pressure increases and that venous pressure varies directly with intrapleural pressure. Kountz was the first to state that the circulatory block in emphysema is not entirely within the pulmonary bed but is also found in the great veins returning blood against a positive intrapleural pressure.

12. Bernoulli, D.: Hydrodynamica, Basil, Switzerland, Argentorati, 1738.

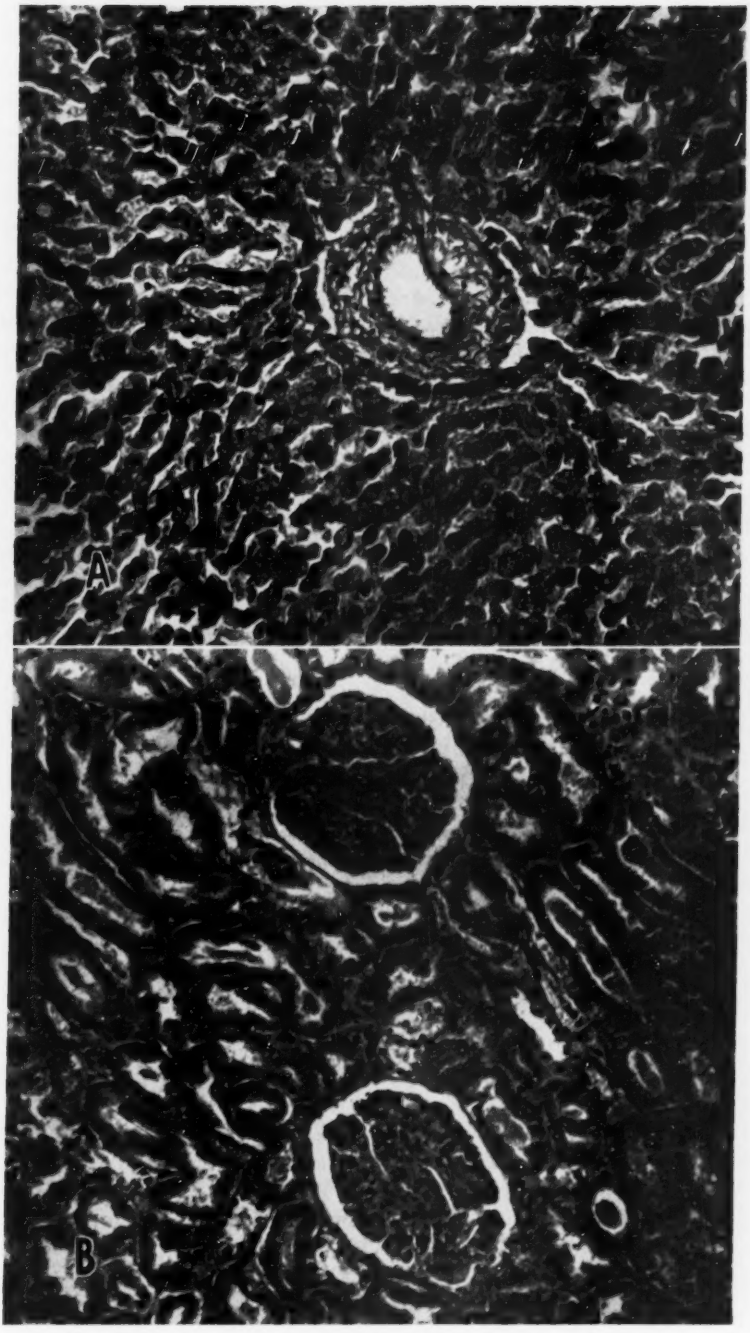

Fig. 11.—Hypertensive renal changes and intact liver from dog shown in Figure 10. *A*, photomicrograph of the liver showing normal hepatic architecture *22* months after portocaval shunt. *B*, photomicrograph of the kidney showing thrombonecrosis in the afferent arterioles and in the glomerular capillary loops after renal wrapping.

Since we have demonstrated that further obstruction to this venous return in the position of recumbent lordosis elevates arterial pressure in emphysema, we believe that such venous obstruction is a primary mechanism in the arterial hypertension.

It therefore appears logical that, applying Bernoulli's principle, it would be possible to decrease the arterial pressure by restoring normal venous velocity to the inferior vena cava. The higher the velocity in the inferior vena cava, the lower the pressure in the renal veins. It should be possible to accomplish this effect by anastomosing the portal vein to the inferior vena cava. Normally the pressure in the inferior vena cava at the renal veins is in the neighborhood of 150 mm. H_2O, whereas the pressure in the portal vein averages 120 mm. H_2O. More important still, the pressure in the vena cava in hypertension is elevated above the normal, whereas the pressure in the portal vein remains normal, since it is protected by the intervening vascular bed of the liver, which lies between it and the inferior vena cava.

Portocaval shunt operations were performed on two dogs previously made hypertensive by wrapping both kidneys in double polythene film, according to the method of Dr. I. H. Page. A van Leersum carotid loop for the recording of future blood pressure had been made. A high portocaval shunt operation was then performed by Drs. Hufnagle, Gillespie, and Popovici, and the laboratory observations were performed by Dr. Popovici. Successive records of the blood pressure were made before and after the kidney-wrapping and at different intervals after the portocaval shunt. These readings, shown below, indicate the hypotensive effect of the portocaval shunt. Both dogs were observed in the hypertensive state several months before the portocaval shunt was performed. After the shunt operation was performed, one dog was followed for 22 months and the other for 14 months. The dog followed 22 months was killed to observe the functioning shunt (Figs. 10 and 11). In this successfully operated dog the mean arterial pressure was 140/135 before renal wrapping and two months prior to the shunt the mean arterial pressure was 172/168. Successive readings after the portocaval shunt was performed were as follows:

(Blood pressure before shunt 172/168)

After 1 month	162/135
After 2 months	125/118
After 3 months	148/133
After 5 months	150/140
After 9 months	120/110
After 12 months	120/110

The liver was not affected by this procedure and showed no degenerative changes after 22 months (Fig. 11).

In the second dog the mean arterial pressure before renal wrapping was 160/154, in May, 1951. Two months after wrapping the reading was 210/190. One month after performing the portocaval shunt the readings were 172/168, 190/182. In this dog there was progressive failure of the portocaval shunt, and the dog died of intestinal obstruction after 14 months. Additional experiments are in progress.

COMMENT

The studies herein presented and the related findings reported by others provide a substantial body of evidence in favor of the conclusion that essential hypertension may result from chronic renal congestion followed by compensatory arteriolar

spasm in the kidney and throughout the arterial tree. The renal congestion is usually secondary to increased intrathoracic pressure associated with emphysema and related pulmonary disease. Increased venous pressure with resultant renal congestion may be augmented by compression of the inferior vena cava in the erect lordotic position, giving rise to combined phrenic and orthostatic hypertension. An additional factor augmenting impeded venous return may be loss of elasticity of superficial tissues resulting from senility or obesity. Ralston and co-workers [13] obstructed the pulmonary artery and the aorta in dogs and found that the veins continued to empty under pressure from a source other than the heart or spleen (the latter did not contract). These authors concluded that elastic forces present in the tissues contribute to the venous outflow or venous return.

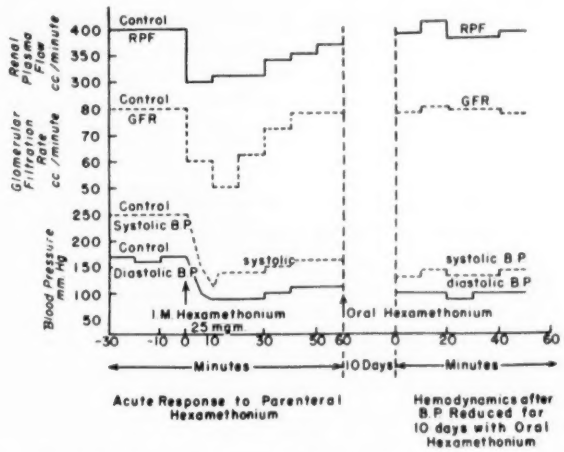

Fig. 12.—Chart showing the adverse effects of antihypertensive drugs on renal function in a patient with hypertension (after Moyer and co-workers [14]).

Hypertension may originate in long-standing (over two years' duration) renal congestion secondary to

1. Loss of intrathoracic pressure in emphysema (complicated by asthma or pulmonary fibrosis)	Phrenic hypertension
2. Compression of vena cava by lumbar lordosis	Orthostatic hypertension
3. Loss of elasticity of subcutaneous tissues (in the obese and elderly)	Subtegmental hypertension

(The congested kidneys react by vasoconstriction, which stimulates generalized vasoconstriction by an unknown mechanism.)

If we assume that arteriolar spasm in the kidneys is the trigger mechanism of the hypertensive kidney, then obliteration of the spasm by sympathomimetic agents such as hexamethonium should improve renal function. Such is not the case (Moyer and co-workers [14]). If we assume, on the other hand, that venous con-

13. Ralston, H. J.; Collings, W. D.; Taylor, A. N., and Ogden, E.: Venous Return in the Absence of Cardiac Drive, Am. J. Physiol. **145**:441, 1945.

14. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. L.: Results with Oral Hexamethonium Alone and in Combination with 1-Hydrazinophthalazine (Apresoline) in the Therapy of Hypertension, Am. J. M. Sc. **225**:379, 1953.

gestion is the trigger mechanism of the hypertensive kidney and that arteriolar spasm is compensatory mechanism to offset this, then (*a*) relaxing the arteriolar spasm with hexamethonium would remove the compensatory mechanism and make renal function worse. This is the case (Fig. 12). (*b*) Increasing the venous congestion by compressing the vena cava would further embarrass the kidney and elevate blood pressure. This is also readily demonstrated (Fig. 6).

Therefore, we conclude that venous congestion is the trigger mechanism for renal reaction in hypertension.

In patients with emphysema, obesity, and faulty posture, the relation of elevated vena cava pressure to hypertension can be demonstrated by (1) the statistical frequency of hypertension in such patients; (2) the elevation of diastolic pressure and the reduction of renal plasma flow by the maneuver of recumbent lordosis; (3) by the relief of hypertension following portocaval shunt in dogs with Page-wrapped kidneys.

If the occurrence of low or subaverage vital capacity in the general population is compared with the facts established in regard to the age, sex, pregnancy, and race incidence of hypertension and its relation to obesity, it is found that the two are well correlated in regard to incidence (Table 8).

TABLE 8.—*Clinical Correlation of Hypertension with Diminished Vital Capacity (V. C.)* and Increased Intrathoracic Pressure*

1.	Hypertension and diminished V. C. are increased in frequency after age 40
2.	Hypertension and diminished V. C. are more common in women
3.	Hypertension and diminished V. C. are more common in the Negro than in the white race, under identical living conditions
4.	Hypertension and diminished V. C. are more common in the obese
5.	Hypertension and diminished V. C. are common in pregnancy

* Diminished vital capacity is a rough index of pulmonary rigidity or loss of negative intrapleural pressure.

Since diminished vital capacity is a rough index of loss of negative intrapleural pressure, we believe that the correlation is significant.

The coexistence of hypertension and emphysema is a common observation. That the two have never been causatively related may be explained by a number of factors. In the first place, the medical profession has accepted the life insurance standard for the upper limits of normal blood pressure, which has been placed as low as 140/80 by some authors and is usually given as 140/90 by most observers. With such low standards, the incidence of hypertension in patients over 40 in the normal population has been placed so high (50% for men and 60% for women) that the usual observer is led to conclude that the coexistence of hypertension with emphysema is purely coincidental. This is particularly true since no statistics are available on the incidence of emphysema in those past middle life and the ability to determine the degree of emphysema in clinical practice is inadequate. Emphysema cannot be judged by the "barrel chest" but must be judged either by diminished reserve air or by limitation of the diaphragmatic excursion.

A second reason for failure to observe the relationship between hypertension and emphysema has been the fact that emphysema may exist for years before hypertension supervenes and only in the latter stages of emphysema is the relationship apparent.

A third reason for the lack of emphasis on this relationship is that postasthmatic emphysema and emphysema complicated by pulmonary fibrosis are more often associated with hypertension than is senile emphysema, which is dependent upon changes in the thoracic cage and loss of elasticity of pulmonic tissues with advancing age. When the asthma or pulmonary fibrosis exists, the clinical attention is directed to the more dramatic pulmonary condition and hypertension is disregarded, since it is usually the borderline type without a systolic blood pressure above 200 mm. Hg.

A fourth reason for lack of emphasis on this relationship is the cyclic nature of the changes. Patients with emphysema and asthma do not have high blood pressure in the initial stage of their disease. Later, a characteristic hypertension may supervene. Still later, low blood pressure is often observed, when myocardial damage supervenes. The latter complication is more frequent than heretofore realized and is left sided rather than right sided in many instances. A single physician rarely observes the entire cycle, because the treatment of the underlying condition of bronchial asthma is unsuccessful in the average clinic and the patient shifts from one doctor to another.

A fifth reason is overemphasis on allergies and the psychosomatic features of bronchial asthma, which has removed a majority of these patients from the careful observation of the internist. The allergist and psychiatrist are not primarily interested in circulatory complications.

Finally (sixth reason) the characteristic borderline hypertension observed in patients with emphysema and asthma has not been heretofore emphasized. This is a form of hypertension in which the diastolic pressure is elevated disproportionately to the systolic. The systolic pressure usually ranges from 170 to 190, whereas the diastolic pressure is usually elevated to 110 to 120 mm. Hg.

CONCLUSIONS

In a study of 60 patients with emphysema over the age of 40 with bronchial asthma of two-or-more years' duration, 28, or 46%, had some degree of arterial hypertension. Using similar standards for the upper limits of normal blood pressure (160/90 mm. Hg), the corresponding percentage of persons with hypertension in the general population is between 20 and 25%. In a series of 15 patients with extrinsic emphysema not complicated by asthma but resulting from such factors as fixation of the chest wall from spondylitis, senility, and osteoarthritis hypertension also occurred, particularly in cases complicated by pulmonary fibrosis or by lordosis in association with abdominal obesity.

It is concluded that long-standing emphysema with loss of negative intrathoracic pressure in patients over 40 can lead to hypertension, particularly when the emphysema is complicated by bronchial asthma or pulmonary fibrosis or when it exists in combination with postural lordosis accompanied by obesity.

Phrenic hypertension appears to be the result of loss of intrapleural negative pressure, with increased venous pressure associated with renal congestion and compensatory arteriolar spasm.

The role of venous congestion as a factor in hypertension can be demonstrated by placing the patient with emphysema in recumbent lordosis, which compresses the inferior vena cava between the posterior edge of the liver and the lumbar spine. In normal persons the blood pressure is either lowered or remains constant. In

persons with hypertension the systolic pressure is slightly elevated and the diastolic pressure is elevated from 15 to 20 mm. Hg or more. The blood pressure in patients with phrenic hypertension is even more markedly elevated if the patients stand upright in a position of lumbar lordosis. It is suggested that bad posture with abdominal obesity added to emphysema is one of the factors with lead to hypertension in overweight persons with moderate emphysema.

It is significant also that when pressure in the inferior vena cava is increased by tilting the patient downward or by his standing in the lordotic position, renal plasma flow is adversely affected as well as diastolic pressure elevated.

Further evidence regarding the role of increased venous pressure in hypertension is submitted on the basis of experiments in dogs. In two dogs rendered hypertensive by wrapping the kidneys according to the Page method, hypertension was relieved for 10 to 22 months, when a portal-caval shunt was performed in these animals, the anastomosis of the portal circulation to the vena cava reducing venous pressure through the Bernoulli effect.

In the present series of persons with emphysema with bronchial asthma there was an unusually large number of cases of myocardial infarction, as determined by electrocardiogram. Three of the patients subsequently died with myocardial infarction. In all, 21 of 60 patients with asthma and emphysema showed some degree of myocardial damage in the electrocardiogram. Fourteen of 25 patients with myocardial damage had both emphysema and hypertension. Seven out of 35 patients without hypertension but with emphysema and asthma had myocardial damage. We believe the mechanism is impaired venous coronary return to the right auricle in the presence of increased intrapleural pressure. The existence of cor pulmonale is a further impediment to coronary outflow. It is significant that both the hypertension and the asthma, and particularly the asthmatic attacks, may improve when these patients are digitalized or given coronary dilators, such as aminophyllin. Finally, myocardial damage, with or without hypertension, as well as a mild degree of chronic anoxemia in patients with severe long-standing emphysema explains the occurrence of left ventricular hypertrophy along with right ventricular hypertrophy which is found at autopsy in such patients.

STUDIES ON NECROTIZING ANGIITIS

IV. Periarteritis Nodosa and Hypersensitivity Angiitis

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CINCINNATI

IN A RECENT report by one of us [1] the various concepts concerning periarteritis nodosa were discussed. The term "necrotizing angiitis" was suggested as a convenient name to use collectively for that group of vascular lesions which are characterized, in their fully developed stage, by fibrinoid necrosis and inflammatory reaction in vessel walls. The term is noncommittal in regard to etiology and is applicable to lesions in either arteries or veins of any caliber and in any location in the body. Previously reported studies on experimentally produced lesions of this nature in rats and dogs [2] and observations of autopsy material in cases of necrotizing angiitis at the Cincinnati General Hospital have demonstrated the feasibility of classifying the necrotizing angiitides into at least five categories. The characteristic morphological features of the vascular lesions of each type have been described in previous reports [3] and are outlined in Table 1.

To employ the term periarteritis nodosa for this heterogeneous group of disease conditions leads to confusion. Its usage for six decades following its origin, in 1866, was confined essentially to cases of the type originally described under that name by Kussmaul and Maier.[4] It was only after the discovery of the role of hypersensitivity that the term was broadened to encompass the microscopic vascular lesions occasionally associated with that condition. Indeed, it is currently applied also to conditions which have little in common with the disease for which the name periarteritis nodosa was originally devised.

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1. Zeek, P. M.: Periarteritis Nodosa: A Critical Review, Am. J. Clin. Path. **22**:777-790, 1952.

2. (*a*) Smith, C. C.; Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs, Am. J. Path. **20**:721-735, 1944. (*b*) Smith, C. C., and Zeek, P. M.: Studies on Periarteritis Nodosa: II. The Role of Various Factors in the Etiology of Periarteritis Nodosa in Experimental Animals, ibid. **23**:148-157, 1947. (*c*) Zeek, P. M.; Smith, C. C., and Weeter, J. C.: Studies on Periarteritis Nodosa: III. The Differentiation Between the Vascular Lesions of Periarteritis Nodosa and of Hypersensitivity, ibid. **24**:889-917, 1948.

3. Zeek.[1] Zeek, Smith, and Weeter.[2c]

4. Kussmaul, A., and Maier, R.: Über eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteriitis nodosa), Deutsches Arch. klin. Med. **1**:484-517, 1866.

TABLE 1.—*Classification of the Necrotizing Angiitides**

Types of Lesions	Associated Clinical Conditions	Duration of Terminal Illness Related to Vascular Lesions	Caliber of Vessels Involved	Sites of Predilection and Distribution	Special Features of Lesions	Other Frequently Associated Lesions	Healed Stage
Hypersensitivity angiitis	Hypersensitiveness to serum, sulfonamides, drugs, etc.	Few days to few weeks; usually less than 1 mo.	Arterioles, venules, capillaries, and small arteries	Kidneys and heart; usually widespread; often in pulmonary vessels and splenic follicular arterioles; uncommon in pancreas and gastroenteric tract	All of about same age; exudative reaction	Interstitial inflammation in viscera; necrotizing glomerular nephritis	Uncertain
Allergic granulomatous angiitis	Asthma and other allergic states with bouts of fever and eosinophilia	Several months to several years	Probably any sized vessel, especially small arteries and veins	Heart; widespread; often in pulmonary vessels and splenic follicular arterioles	Various ages; necrosis of eosinophilic exudate; multinucleated giant cells; granulomas	Granulomas in extravascular connective tissues and serous membranes; Loeffler's pneumonia; sequelae of vascular obstruction	Nonspecific scarring
Rheumatic arteritis	Fulminating rheumatic fever	Masked by rheumatic carditis	Small arteries and occasionally veins	Heart and lungs; occasionally widespread; uncommon in pancreas and gastroenteric tract	Associated with Aschoff bodies; otherwise simulates hypersensitivity angiitis	Rheumatic carditis, pneumonitis, and aortitis	Nonspecific scarring
Periarteritis nodosa	Polyneuritis, fever and "multiple systems disease," usually with hypertension	Several months to a year or more	Small and medium sized muscular-type arteries near hili of viscera, in striated muscles, and near peripheral nerves	Bifurcations and branchings; common in wall of gastroenteric tract, near mesenteric attachment, in pancreas and kidneys; often widespread; usually absent in pulmonary vessels and splenic follicular arterioles	Various ages; proliferation precedes exudation in adventitia; forms granulation tissue; prone to form small aneurysms	Sequelae of hypertension and vascular obstruction	Marked distortion of vessels; scars sweeping through segments of wall with focal rupture of media; aneurysms
Temporal arteritis	Pain over involved vessels, malaise, fever, anorexia	Nonfatal	Temporal and other cranial arteries	Temporal arteries	Multinucleated giant cells; no tubercles; no aneurysms	Cellulitis of contiguous tissues	Spontaneous regression or nonspecific scarring

* Revised from table in Zeek.[1]

The present study is concerned with the various clinical manifestations which may aid in the differential diagnosis of the two most common types of necrotizing angiitis, namely, periarteritis nodosa and hypersensitivity angiitis.

METHODS

During the last two decades vascular lesions which fulfilled the criteria for necrotizing angiitis were found at autopsy in 60 cases at the Cincinnati General Hospital, Children's Hospital, and Drake Memorial Hospital. Of these, 35 were classified pathologically as periarteritis nodosa, and 10 as hypersensitivity angiitis. These 45 cases provided the data for the present study. The remaining 15 cases, to be reported later, included those which fell into other rarer categories of necrotizing angiitis and those wherein the available material was insufficient for differential diagnosis.

The cases of the present series were grouped according to the types of vascular lesions found at necropsy; the clinical records were analyzed and charts were made, listing in each case the signs, symptoms, and pathological lesions related to each of the major systems of the body. This procedure provided a means for contrasting the clinical findings associated with the two selected types of necrotizing angiitis.

OBSERVATIONS

There were certain striking differences between the clinical findings in the group of cases designated periarteritis nodosa and those in the group of cases called hypersensitivity angiitis. Moreover, the cases of periarteritis nodosa were found to be divisible clinically into two subgroups, although there seemed to be no morphological differences in the lesions except such as were attributable to variations in the duration of the disease process. In the first subgroup, of 14 cases, the nodular vascular lesions of the Kussmaul-Maier type [4] were unassociated with any other major disease process and the periarteritis nodosa had progressed during a known period of illness of from 1 to 12 months to a fatal termination.

In the second subgroup, consisting of 21 cases, the lesions of periarteritis nodosa had developed shortly before death in patients suffering from severe renal disease and/or hypertension. The lesions appeared to be identical morphologically with the more acute lesions of periarteritis nodosa. In cases in which malignant hypertension was present the lesions of periarteritis nodosa could be readily differentiated from arteriolar necrosis by location and appearance. The former occurred at the sites of branching and bifurcation of muscular-type arteries and were characterized by striking inflammatory reaction as well as by fibrinoid necrosis. In contrast, the necrotizing lesions of malignant hypertension involved arterioles and the inflammatory reaction was minimal or absent.

In Tables 2 and 3 the 45 cases of the present series are grouped according to the type of necrotizing angiitis found at autopsy and the clinical manifestations are tabulated. For ease of identification, the first and second subgroups of periarteritis nodosa will be referred to as primary and secondary periarteritis nodosa, respectively. It is not to be assumed that the term secondary necessarily connotes dependence on renal disease or hypertension per se as the cause of the vascular lesions.

General Aspects of Cases (Table 2)

Age.—All the 45 patients were over 20 years of age at the time of death except three with secondary periarteritis nodosa (ages 8, 13, and 14 years) and 1 with hypersensitivity angiitis (age 8 years). In the present small series of cases no significance could be attached to the slight differences in age among the three groups.

Sex.—Although necrotizing angiitis seemed to be more common in males than in females, the difference was not as great as the figures in the Table would indicate, since in the autopsy population from which these cases came the ratio of males to females was probably about 2:1. This ratio was found on random sampling. Exact figures for the 20-year period have not been determined. Nevertheless, primary periarteritis nodosa seems to be preponderantly a disease of adult males.

Duration.—Primary periarteritis nodosa was found to be a disease of long duration characterized by remissions and exacerbations. At autopsy the vascular lesions were in all stages of formation and healing, indicating repeated crops of new lesions over periods of many weeks. In marked contrast, hypersensitivity angiitis was a disease of short duration, with all lesions in a given case appearing to be of about the same age. Nine patients died within two weeks of the onset of the signs and symptoms which were attributable to the vascular lesions or to the hypersensitive state. The single exception was an 8-year-old girl who lived 32 days after the onset of symptoms. In this case the vascular lesions were more extensive and showed beginning chronicity. Certain features of the lesions resembled those of early disseminated lupus erythematosis, namely, beginning fibroblastic activity around

TABLE 2.—*General Aspects of Cases*

	Cases, No.	Age Range, Yr.	Sex		Estimated Duration	Established Hypertension	History of Recent Sulfonamide Therapy	History of Allergy
			M	F				
Primary periarteritis nodosa.....	14	28-64	13	1	5 to 52 wk.	10 of 12*	0	1
Secondary periarteritis nodosa....	21	8-77	12	9	Unknown	21	2 of 19	0
Hypersensitivity angiitis	10	8-79	8	2	6 to 32 days	3	7	0

* Adequate history available in 12 cases only.

necrotic follicular arterioles in the spleen and beginning "wire loop" degeneration in partially necrotic renal glomerular tufts. In the cases of secondary periarteritis nodosa the onset of the vascular lesions was masked by the severe renal disease and hypertension.

Hypertension.—In 3 of the 10 cases of hypersensitivity angiitis there was hypertensive cardiovascular disease which antedated the onset of necrotizing angiitis, an incidence which is no greater than would be expected in any random group of patients of similar age and sex. In contrast, the high incidence of established hypertension in the two groups of cases of periarteritis nodosa indicates a significant association of the two conditions.

In the present series hypertension was a prominent feature of the clinical picture in each of the 21 cases of secondary periarteritis nodosa and was in a malignant phase at the time of death in at least 15 cases. In 10 of the 14 cases of primary periarteritis nodosa there was established hypertension before the onset of the symptoms of necrotizing angiitis. In two cases repeated examinations both before and after the estimated time of onset of periarteritis nodosa revealed no elevation of blood pressure. In the other two cases, in which there was no hypertension while the patients were in the hospital, the past histories were inadequate in regard to blood pressure. Neither clinical nor pathological evidence of malignant hypertension was found in any case of the primary group.

Sulfonamides and Allergy.—There was no record of sulfonamide therapy in any case of primary periarteritis nodosa prior to the onset of the disease. In 9 of the 14 cases death had occurred before sulfonamides had come into clinical usage. No history of serum administration or exposure to other antigenic agents was obtained except in one case, that of a patient who had received gold therapy for rheumatoid arthritis four months prior to admission. With respect to allergy, one patient had been afflicted with seasonal asthma for many years, although asthma was not manifested while he was in the hospital. In the group of cases of secondary periarteritis nodosa the records in 19 were sufficiently complete to reveal that only two patients had received sulfonamide early in their illness. In no case was there a history of allergy.

On the other hand, in 7 of the 10 cases of hypersensitivity angiitis, there seemed to be a direct relation between sulfonamide therapy and the onset of symptoms. In the other three cases a specific antigen was not found. There was no history of previous allergy in any case.

Report of Cases

Case 180634.—A 53-year-old white man was admitted March 25, 1944, for hematuria. Marked urethral strictures were demonstrated. On April 16, following dilatation, chills and fever developed. Sulfadiazine was administered, 1.0 gm. every four hours. Blood cultures revealed nonhemolytic Staphylococcus albus. On April 22 diffuse petechiae appeared. Sulfadiazine was discontinued and penicillin instituted. Blood cultures remained negative from then on, but fever continued. On April 30 sulfadiazine was readministered, 1.0 gm. every four hours. On May 4 the patient died. Autopsy revealed acute bacterial endocarditis, diffuse hypersensitivity angiitis, and visceral lesions, which were associated with these two conditions. In this case there were also lesions of hypertensive cardiovascular disease, which antedated the terminal illness.

Case 24604.—A 79-year-old white man was admitted Oct. 22, 1944, with pneumonia. An upper respiratory infection had developed 10 days before admission. During this period he was given sulfathiazole twice. Each time it was discontinued because of a severe headache. On the day before admission a rash developed on the back of the hands and legs. Following admission the patient received sulfamerazine, 3.0 gm. intravenously initially and 1.0 gm. by mouth every eight hours. On Oct. 25, because of increasing blood urea nitrogen, the sulfamerazine was discontinued. On Oct. 30 the patient died. Autopsy revealed lobular pneumonia, diffuse hypersensitivity angiitis, necrotizing glomerulitis, and uremic pericarditis.

Case 188431.—A 48-year-old Negro man was admitted Jan. 10, 1946, for chronic osteomyelitis of the tibia. He had received sulfadiazine in 1943. On Feb. 2 he was given sulfadiazine, 1.0 gm. every four hours. On Feb. 7, his temperature rose from normal to 102 F. and continued to be elevated. On Feb. 9 cough and asthmatic dyspnea were noted. This condition continued till death. On Feb. 14 the blood urea nitrogen was 105 mg. per 100 cc. The patient died the next day. At necropsy there was diffuse hypersensitivity angiitis, with associated visceral changes, and established hypertensive cardiovascular disease.

Case 218162.—A 69-year-old white man was admitted Sept. 28, 1946, for cerebral thrombosis. He was given sulfadiazine, 1.0 gm. every four hours, because of pneumonia. Fever present on admission continued throughout his course. On Oct. 5 the sulfadiazine was discontinued and penicillin was prescribed. On Oct. 7 oliguria developed which continued until death, on Oct. 12. Necropsy revealed diffuse hypersensitivity angiitis with associated visceral changes including acute diffuse necrotizing glomerulitis.

Case 227495.—A 46-year-old white man was admitted July 12, 1947, with Staphylococcus septicemia. He was given penicillin, and sulfadiazine 4.0 gm. initially and 1.5 gm. every four hours. On July 14, because of oliguria, the sulfadiazine was discontinued. With remission of the oliguria, on July 21, this therapy was reinstituted in dosage of 1.0 gm. every six hours.

The next day streptomycin was added. On July 28 the sulfadiazine was discontinued. Fever continued unabated, and the patient died on Aug. 4. Autopsy revealed evidence of sepsis and hypersensitivity angiitis.

Case 254604.—A 62-year-old white man was admitted Aug. 4, 1949, with carcinoma of the rectum. He was prepared for bowel surgery with sulfasuxidine, 2.0 gm. every four hours. On Aug. 11 the operation was successfully performed. Sulfasuxidine was discontinued, and penicillin and streptomycin were administered. On Aug. 20 oliguria developed, and the patient died the next day. Necropsy revealed hypersensitivity angiitis with associated visceral changes.

Case 256966.—A 46-year-old white man was admitted Nov. 30, 1949, acutely ill with fever and a rash. Five days before admission he took an unknown amount of a sulfonamide. His condition rapidly worsened and he died three days after admission. Necropsy revealed chronic pancreatitis and hypersensitivity angiitis, with the immediate cause of death being hemorrhage into the gastroenteric tract from ulcerative esophagitis.

Clinicopathological Correlations (Table 3)

Table 3 depicts the various clinical manifestations and the distribution of the vascular lesions in relation to anatomic structures. The signs and symptoms of necrotizing angiitis were frequently difficult to evaluate, since they were often masked by those of hypertensive cardiovascular disease, renal disease, and various infectious processes. Consequently, the clinical findings listed in the Table were not always those of necrotizing angiitis alone but probably were a result of that condition combined with other pathological processes.

Fever.—Fever was common in all groups. In the cases of primary periarteritis nodosa it tended to be of low-grade type and appeared to depend on the amount of tissue which was undergoing infarction. In the cases of secondary periarteritis nodosa the lesions of necrotizing angiitis were less extensive and fewer in number. Fever was less frequent and appeared to be associated chiefly with the lesions of malignant hypertension or in some cases with concurrent infectious processes. Fever was present in all of the patients with hypersensitivity angiitis and was probably caused chiefly by hypersensitivity, although concurrent infections again were common.

Eosinophilia.—Whenever 4% or more eosinophiles were present in blood films, eosinophilia was considered to be present. It was found in 6 of 11 cases of primary periarteritis nodosa in which counts were made. In five of the cases the counts were sufficiently dispersed throughout the patient's course to indicate that eosinophilia was of irregular occurrence in this condition. There seemed to be a tendency for eosinophilia to appear, remain for a few weeks, and then disappear. The highest count was 14%. Eosinophilia was not correlated with the severity of the disease, since it was frequently absent in counts made nearest the time of death.

Among the cases of secondary periarteritis nodosa, 18 patients had differential counts, but in each of 10 cases only one count was recorded. In each of the other eight cases, two to nine counts were made. In these 18 cases, eosinophilia was found only once, and that appeared in the third of six counts interspersed over the last month of life of one patient. Although too few counts were made to warrant conclusions, it seems probable that eosinophilia is rare in secondary periarteritis nodosa.

In the cases of hypersensitivity angiitis, eosinophilia appeared only once, and that was two days before death in the patient who lived the longest (32 days) after the onset of the illness.

TABLE 3.—*Clinicopathological Correlations*

	Group 1 Primary Periarteritis Nodosa (14 Cases)*			Group 2 Secondary Periarteritis Nodosa (21 Cases)*			Group 3 Hypersensitivity Angiitis Angiitis (10) Cases)*		
	Clinical Manifest.	Vascular Lesions	Path. Findings	Clinical Manifest.	Vascular Lesions	Path. Findings	Clinical Manifest.	Vascular Lesions	Path. Findings
Fever	12	..	..	12 of 19	..	..	10	..	..
Eosinophilia	6 of 11	..	..	1 of 19	..	..	1 of 8	..	..
Heart	..	13	..	..	4	..	..	4	..
Congestive failure	5	..	5	4	..	7	1	..	0
Gross infarction	2	..	3	0	..	0	0	..	0
Lungs	..	0	..	..	0	..	..	4	..
Necrotizing pneumonia	0	..	0	0	..	0	3	..	3
Asthma	0	..	..	0	..	..	1	..	..
Gastroenteric tract	..	13 of 13	..	..	17 of 19	..	..	3 of 7	..
Pain	9	..	..	5	..	..	1	..	..
Hemorrhage	3	..	..	4	..	..	0	..	1
Ulceration	..	..	6	..	..	9	..	..	4 of 7
Perforation	2	..	2	0	..	0	0	..	0
Gallbladder	..	9 of 9	..	..	5 of 11	..	..	1 of 2	..
Cholecystitis	2	..	5 of 9	0	..	7 of 11	0	..	1 of 2
Gangrene	..	..	1 of 9	..	..	2 of 11	..	..	0
Pancreas	..	11 of 12	..	..	10 of 20	..	..	1	..
Infarction	2	..	7 of 12	1	..	3 of 20	0	..	0
Hyperglycemia	4 of 6	..	..	..	..	..	..	..	..
Liver	..	11	..	..	2	..	..	7	..
Infarction	..	..	2	..	..	1	..	..	0
Nervous system	..	..	..	..	..	..	..	..	..
Central	1	5 of 7	7 of 7	0	2 of 5	5 of 5	1	2 of 4	3 of 4
Peripheral nerves	9	6 of 7	..	0	No sections		0	No sections	
Skin	4	..	..	3	..	..	4	..	..
Joints	0	..	..	0	..	..	2	..	..
Muscle	11?	8 of 8	..	..	2 of 6	..	..	0 of 4	..
Spleen	..	2	..	..	1 of 20	..	..	7	..
Infarction	..	..	1	..	..	2	..	..	1
Adrenal gland	..	12 of 13	..	..	9 of 20	..	..	5 of 8	..
Infarction	..	..	7 of 13	..	..	4 of 20	..	..	1 of 8
Genital organs	..	..	..	..	..	..	..	..	..
Testis and epididymis	..	6 of 6	..	..	4 of 6	..	..	2 of 2	..
Ovary	..	..	..	..	3 of 5	..	..	..	..
Orchitis	1	..	4 of 6	0	..	1 of 6	0	..	1 of 2
Epididymitis	2	..	..	0	..	..	0	..	..
Kidney and urinary tract	..	14	..	..	10	..	..	10	..
Hematuria	..	..	..	..	..	..	..	..	..
Microscopic	5 of 13	..	..	9	..	..	3	..	..
Macroscopic	0	..	..	9	..	..	2	..	..
Renal edema	0	..	..	4	..	..	1	..	..
Oliguria	0	..	..	3 of 15	..	..	1	..	..
Azotemia	4 of 9	..	..	4	..	..	3	..	..
Uremia	0	..	..	17	..	..	4	..	..
Renal infarcts	..	..	8	..	..	3	..	..	0
Malignant nephrosclerosis	..	..	0	..	..	17	..	..	0
Glomerulonephritis	..	..	0	..	..	6	..	..	9
Pyelonephritis	..	..	2	..	..	5	..	..	2

* Unless otherwise stated data were available in all cases.

Heart.—Necrotizing angiitis was found in the myocardium in 13 of the 14 cases of primary periarteritis nodosa and resulted in gross myocardial infarction in 3 cases. In one of these the infarct caused death, in a second case chronic congestive failure developed, and in the third the myocardial infarct was unsuspected and the patient died of concomitant cerebral infarction due to periarteritis nodosa. In three additional cases small myocardial infarcts were found microscopically. Five of the 14 patients of this group suffered from congestive cardiac failure, but in only one case could the necrotizing vascular lesions account for all of the pathological changes in the myocardium. In the other four cases cardiac failure was ascribed to hypertensive cardiovascular disease.

In the cases of secondary periarteritis nodosa, cardiac failure, when present, was attributed entirely to hypertensive cardiovascular disease, although in 4 of the 21 cases there was early necrotizing angiitis in the myocardium.

The one patient with hypersensitivity angiitis and cardiac failure is of unusual interest since the heart failure was attributed entirely to multiple miliary infarcts in the myocardium caused by hypersensitivity angiitis. In three other cases hypersensitivity angiitis was present, but in insufficient degree to produce symptoms.

Lungs.—The absence of necrotizing angiitis in the pulmonary arteries in cases of general systemic periarteritis nodosa and its frequent presence in cases of hypersensitivity angiitis have often been discussed by various investigators.[5] Its significance awaits further study. In our total series of 60 cases of necrotizing angiitis there were 2 cases in which the vascular lesions were limited to the pulmonary circulation, and in each there was cause for pulmonary hypertension. These cases will be presented in another report and are not included in the present series of 45 cases.

An unusual type of necrotizing pneumonia was found in three cases of hypersensitivity angiitis. In one of them there was, in addition, the formation of a fibrinoid membrane within the alveolar sacs. Auscultation revealed rhonchi and rales but no consolidation. Roentgenography presented the pattern of pulmonary edema in one case and lobular pneumonia in another. In one patient with hypersensitivity angiitis severe bronchiolar spasm developed before death. Roentgenography showed no abnormality. At autopsy there was extensive necrotizing angiitis but no pneumonia. The only history of asthma was in one case of primary periarteritis nodosa, the patient having had seasonal attacks for many years, but no asthma was noted during the illness in the hospital.

Gastroenteric Tract.—Abdominal pain was a common complaint in cases of primary periarteritis nodosa and was easily explained by the extent of the vascular lesions in the medium-sized mesenteric arteries. In patients with secondary periarteritis nodosa pain was less common and vascular lesions were less extensive. Only one patient with hypersensitivity angiitis complained of abdominal pain, which was epigastric in location. At necropsy there were multiple pin-point gastric erosions associated with necrotizing angiitis in submucosal vessels.

Gross hemorrhage into the gastroenteric tract occurred in three cases of the first group, in four of the second group, and was found at necropsy in one case of the

5. (*a*) Boyd, L. J.: The Pulmonary Manifestations of Periarteritis Nodosa (Conclusion), Bull. New York M. Coll. **7**:94, 1944. (*b*) Ophüls, W.: Periarteritis Acuta Nodosa, Arch. Int. Med. **32**:870-898, 1923. (*c*) Zeek.[1] (*d*) Zeek, Smith, and Weeter.[2c]

third group. In the cases of primary periarteritis nodosa the hemorrhages were associated with ulcerations caused by vascular lesions in the jejunum or colon. In secondary periarteritis nodosa ulcerations of the gastroenteric tract were found in nine cases, the most frequent sites again being jejunum and colon. In this group ulceration was attributed to a combination of periarteritis nodosa and marked arteriolar sclerosis and necrosis, the latter associated with malignant hypertension.

Although ulcerations of the gastroenteric tract were found in four cases of hypersensitivity angiitis, they were unrelated to the vascular disorder. In two cases they were associated with septicemia. In another there was ulcerative esophagitis with massive hemorrhage, but no necrotizing angiitis was found in the lesion. In the fourth case there was peptic ulceration of aberrant gastric mucosa in a Meckel's diverticulum.

Enteric perforation occurred in two cases of primary periarteritis nodosa. In one the patient was thought to have a perforated peptic ulcer but surgery revealed infarction of a large segment of jejunum. In the other case there was perforation of the colon, with pelvic peritonitis. In no case of hypersensitivity angiitis were the vascular lesions of sufficient extent to cause hemorrhage or perforation, and the latter did not occur in any case of secondary periarteritis nodosa.

Gallbladder.—There were such extensive vascular lesions in the gallbladders of two patients with primary periarteritis nodosa that acute cholecystitis was manifested clinically. In one case the condition had progressed to perforation and peritonitis, and gangrene of the wall had resulted in sloughing of a large strip of mucosa, which at necropsy was found plugging the ampulla of Vater. In the second group cholecystitis was not recognized clinically although it was found at necropsy in seven cases, in five of which there were associated vascular lesions. In two cases there was beginning gangrene of the gallbladder. Sections of this structure were available in only two cases of hypersensitivity angiitis, in one of which were presented both cholecystitis and vascular lesions, but the former condition was chronic and antedated the latter.

Pancreas.—Vascular lesions were frequent in the pancreas in both primary and secondary periarteritis nodosa but were found in only one case of hypersensitivity angiitis. In seven cases of primary periarteritis nodosa pancreatic infarcts were caused by the vascular lesions. In two cases massive pancreatic necrosis had produced related symptomatology. Glucose tolerance curves revealed hyperglycemia in four of six cases of this group. In two of these cases there was glycosuria, but not severe enough to require insulin. In the second group vascular lesions were found in the pancreas in 10 cases, in 3 of which there were pancreatic infarcts. In one of these massive necrosis had caused shock and death. No glucose tolerance tests were done in this group. The pancreatic vascular lesions found in the one case of the third group were minimal.

In contrast to the findings in cases of both primary and secondary periarteritis nodosa, vascular lesions in cases of hypersensitivity angiitis were absent or minimal in all sections of the gastroenteric tract, pancreas, and gallbladder, and the only related symptomatology recorded was in the patient with gastric erosions cited above.

Liver.—In primary periarteritis nodosa the larger arteries of the portal areas were involved in 11 of 14 cases. In two cases extensive infarction had occurred but no related symptomatology was recorded. Necrotizing angiitis was present in two cases of the second group, with infarction in one. In hypersensitivity angiitis there were hepatic vascular lesions in 7 of the 10 cases. Not only were lesions found in hepatic arterioles of the triads, but occasionally there were inflammation and fibrinoid necrosis of portal venules. No infarcts of the liver were found in this group.

Nervous System.—In seven cases of primary periarteritis nodosa microscopic sections of the central nervous system were available for study. Necrotizing vascular lesions were present in five of them. The lesions occurred in meningeal vessels of the brain and spinal cord. In one case there was involvement of the arteries in the choroidal coat of the eye and in the muscles of the eyeball. Encephalomalacia of various extent was common in this group of cases, but it was usually difficult to separate the effects of necrotizing angiitis from those of hypertension and atherosclerosis. In one case, however, an area of softening, large enough to be manifested clinically, was caused by periarteritis nodosa. In each of the other two groups very few sections of the central nervous system were available for study, but in two cases of each group necrotizing vascular lesions were found in the sections available. One patient with hypersensitivity angiitis had convulsions, and no cause other than necrotizing angiitis was encountered.

Peripheral neuritis occurred commonly in primary periarteritis nodosa, being manifested clinically in 9 of the 14 cases. Sensory and motor abnormalities occurred with equal frequency. At necropsy sections of peripheral nerves and their perineural stroma showed periarteritis nodosa in six of the seven cases examined. There were no clinical manifestations of peripheral neuritis in the other two groups of cases, and no sections of peripheral nerves were available for study.

Skin.—Four patients with primary periarteritis nodosa presented skin lesions. In one case there were pityriasis-rosea-like lesions on the trunk, followed by vesicles and bullae on the extremities. In another patient a macular-papular rash developed on the trunk, with scattered purpuric lesions on the extremities. The other two patients had only purpuric lesions on the lower extremities. It is of interest that two of these four patients had beefy red nonpainful tongues and another patient had similar tongue changes but no skin lesions. Unfortunately, no sections from these involved areas were taken for pathological study.

Among the cases of secondary periarteritis nodosa, three patients presented purpuric manifestations, and one of these also had areas of maculopapular eruption on the trunk. These three patients had uremia, which may have caused the purpura. Sections were not available for pathological examination.

Four patients with hypersensitivity angiitis had skin rashes. In two there was purpura of the extremities, and one of these had a butterfly erythema of the face. The other two had generalized maculopapular eruptions; one of these also had large bullae on his arms.

Subcutaneous nodules were not observed in any of the groups.

Joints.—Only two patients had symptoms related to joints. Both of these were in the third group. In one case there was swelling of a wrist. X-ray showed only

an effusion in the joint. In the other case there was moderate acute inflammation in the proximal phalangeal and metacarpophalangeal joints of one hand. No sections of joints were available.

Muscle.—Tenderness in muscle areas was manifested in 11 cases of primary periarteritis nodosa, but it could not be ascertained how much of this was due to neuritis. Of five satisfactory biopsies, all revealed characteristic vascular lesions. At necropsy striated muscle was examined microscopically in eight cases and all showed vascular lesions. Muscle tenderness was not noted in either of the other groups, and no biopsy specimens were taken. At necropsy sections of muscle were taken in six cases of secondary periarteritis nodosa, two of which showed vascular lesions. Of the cases of hypersensitivity angiitis, none of four showed vascular lesions in sections of muscle.

Hemopoietic System.—In only two cases of periarteritis nodosa was there necrotizing angiitis in the spleen. The lesions involved the larger arteries near the hilum. Probably more lesions would have been found if more sections had been taken from this region. In experimentally produced periarteritis nodosa [26] the lesion rarely extends into follicular arterioles except those very near the hilum. In contrast, in 7 of 10 cases of hypersensitivity angiitis there were lesions in the follicular arterioles. Usually only a few vessels were involved, but in the one case with survival for 32 days after the onset of the illness nearly all of the follicular arterioles presented lesions. Too few sections of lymph nodes and bone marrow were available to permit comparisons between the groups. In the cases of primary periarteritis nodosa and hypersensitivity angiitis a mild anemia frequently developed as the disease progressed. In the cases of secondary periarteritis nodosa more marked anemia was associated with the severe renal disease. Frequent leucocytosis was associated with infections and necrotizing lesions. Eosinophilia has been discussed above.

Endocrine Organs.—The small arteries around the adrenals were common sites for lesions of both primary and secondary periarteritis nodosa, and in 11 cases they were associated with infarcts. No clinical manifestations were recognized. In five cases of hypersenstitivity angiitis smaller vessels within the adrenal (usually capillaries and venules) and in the periadrenal adipose tissue presented lesions but again there was no clinical symptomatology referable to this region.

Ovaries, testes, and epididymides were common sites for lesions of primary periarteritis nodosa. In three cases there were clinical findings indicating inflammatory disease in the scrotum. Autopsy also revealed necrotizing angiitis in the other two groups, but no clinical signs were manifested.

Kidneys and Urinary Tract.—The four important kinds of renal lesions found at necropsy in these 45 cases of necrotizing angiitis were infarcts, malignant nephrosclerosis, glomerulonephritis, and pyelonephritis. There was a significant difference in incidence of these lesions in the three groups. Renal infarcts were common in primary periarteritis nodosa and were caused by the vascular lesions but were not extensive enough to cause renal insufficiency. Other forms of renal disease were uncommon. In hypersensitivity angiitis the predominating renal lesion was acute necrotizing glomerulonephritis, being present in 9 of the 10 cases. Renal infarcts were not found in this group. Among the cases of secondary periarteritis nodosa

malignant nephrosclerosis was the most frequent type of renal disease, being an important factor in causing uremia in at least 13 cases. However, other forms of renal disease had frequently preceded the onset of the malignant phase of hypertension, as will be discussed later.

Repeated microscopic hematuria occurred in 5 of 13 cases of primary periarteritis nodosa and was related to renal infarcts. Moreover, in one patient vascular lesions led to necrosis of the bladder wall and pelvic peritonitis. In this group there was no record of grossly bloody urine at any time. In contrast, gross blood was found in the urine of nine patients with secondary periarteritis nodosa. In two of these the bleeding was attributed to glomerulonephritis. In the other seven cases severe arteriolar necrosis associated with malignant hypertension had caused extensive necrosis of glomerular tufts and erosions of the mucosa in the renal pelves and ureters, thus giving rise to gross hematuria. In no case was the bleeding found to occur from the larger vessels which showed periarteritis nodosa.

The high incidence of gross hematuria in cases of malignant hypertension in which the lesions of periarteritis nodosa were being initiated is considered to be of diagnostic significance. In a control group of 30 cases of malignant hypertension and arteriolar necrosis, which were uncomplicated by periarteritis nodosa, gross hematuria was noted only twice. It seems that periarteritis nodosa may be anticipated in cases of malignant hypertension in which arteriolar necrosis is so severe that it causes gross hematuria, but the explanation for this occurrence awaits further investigation.

Hematuria was recorded in five cases of hypersensitivity angiitis, being microscopic in three and of macroscopic degree in two. Although vascular lesions were present in the arterioles, venules, and capillaries of the interstitial tissues in all cases, the hematuria was attributed to other renal lesions. These were chiefly glomerulonephritis of a peculiar necrotizing type, which was present in nine cases of this group. This lesion has been described and illustrated in a previous report.[2e]

Nephrotic type of edema was present in four cases of secondary periarteritis nodosa in which the underlying renal lesion was subacute proliferative glomerulonephritis. The one case of hypersensitivity angiitis with renal edema was that of an 8-year-old girl, who lived 32 days after the onset of her illness, during which time a typical nephrotic syndrome developed, with edema, albuminuria, and low serum proteins. At necropsy there was diffuse necrotizing glomerulonephritis which was becoming subacute. A few glomerular tufts presented beginning crescent formation, while a few others had an appearance similar to the "wire loop" formations of disseminated lupus erythematosus. Renal edema was not noted in any case of primary periarteritis nodosa.

Oliguria was reported in three cases of secondary periarteritis nodosa. The cause was thought to be renal tubular degeneration secondary to glomerular and arteriolar necrosis. In one case of hypersensitivity angiitis oliguria was the initial symptom of the disease.

The terms azotemia and uremia are used in Table 3 to indicate degrees of renal insufficiency. Azotemia connotes an elevated blood urea nitrogen below 80 mg. per 100 cc. without significant symptoms of renal insufficiency. The term uremia is used when the signs of the uremic syndrome were manifested and the blood urea nitrogen

usually exceeded 80 mg. per 100 cc. In a few cases the diagnosis of uremia was made on the former findings together with the pathologist's report, since there were no records of the blood urea nitrogen during the last few days of life.

Azotemia occurred in four of nine adequately tested patients with primary periarteritis nodosa. In two there was moderate nephrosclerosis, and in the other two the patients suffered from severe shock. Uremia did not occur in this group.

Since the cases designated secondary periarteritis nodosa were those with severe renal disease, it is not surprising that there was azotemia in 4 and uremia in 17 cases. The cause of renal insufficiency in each case was the underlying renal disease rather than periarteritis nodosa. The latter, though present in the kidneys in 10 of the 21

TABLE 4.—*Types of Renal Disease in Secondary Periarteritis Nodosa*

Renal Disease at Autopsy	Case No.	Malignant Phase of Hypertension at Time of Death	Last Blood Urea Nitrogen		Renal Edema	Cause of Death
			Mg./100 Cc.	Days Before Death		
Predominantly malignant nephrosclerosis (other renal disease minimal or absent)	CGH 70383	Present	60	6	Absent	Uremia, cerebral hemorrhage
	CGH 212510	Present	150	0	Absent	Uremia
	CGH 154621	Present	125	2	Absent	Uremia, pancreatic necrosis
	CGH 216638	Present	75	0	Absent	Uremia, hypertensive encephalopathy
	CGH 250819	Present	240	1	Absent	Uremia
	CGH 266852	Present	23	2	Absent	Sudden death during spinal anesthesia
	CH 63441	Present	NPN 82	1	Absent	Gangrene of intestine
	CGH 192820	Present	177	2	Absent	Uremia
	CGH 243691	Present	175	1	Absent	Uremia
	CGH 112473	Present	142	1	Absent	Uremia
Chronic pyelonephritis with superimposed malignant nephrosclerosis	CGH 175036	Present	160	0	Absent	Uremia
	CGH 222614	Present	230	5	Absent	Uremia, hypertensive encephalopathy
	CGH 158299	Present	180	2	Absent	Uremia
	CGH 6337	Present	90	6	Absent	Uremia, hypertensive encephalopathy
	CGH 177991	Absent	144	3	Absent	Uremia, pyemia
Chronic glomerulonephritis (malignant nephrosclerosis terminal or minimal)	CGH 148338	Present	130	1	Absent	Uremia
	DMH 46-204	Absent	45	6	Present	Unknown
	CH 32377	Absent	102	3	Present	Uremia
	CH 80343	Absent	NPN 234	1	Present	Uremia
	CGH 201464	Absent	250	?	Present	Uremia
Marked "benign" vascular nephrosclerosis; minimal arteriolar necrosis	CGH 4994	Absent	52	13	Absent	Cerebral thrombosis

cases, was not advanced sufficiently to produce infarcts except in 3 cases, and in these there were other factors which contributed to vascular occlusion.

Similarly, in the group of cases designated hypersensitivity angiitis renal insufficiency was prominent. Although the vascular lesions were often severe, the most important cause of renal failure was acute necrotizing glomerulonephritis, which probably represented an extension of the vascular lesions into the glomerular tufts. In two cases there was also focal pyelonephritis. The necrotizing glomerular lesions varied in extent from minimal focal lesions in only a few tufts to widespread bilateral lesions which caused uremia and death.

TYPES OF RENAL DISEASE IN SECONDARY PERIARTERITIS NODOSA (TABLE 4)

In Table 4 are given clinical and pathological aspects of the renal disease found in the group with secondary periarteritis nodosa. In 10 of the 21 cases malignant nephrosclerosis was the only important renal disease present. Malignant nephro-

sclerosis was diagnosed pathologically when there was necrosis of renal arterioles and glomerular tufts with minimal or no inflammatory reaction, the type of lesion described by Goldblatt and co-workers.[6] In a few of these cases there were also small foci of healed pyelonephritis or of "benign" vascular nephrosclerosis. In one case there were a few scattered glomeruli with adhesions between the tufts and the capsules, suggesting minimal healed glomerulonephritis.

In five other cases malignant nephrosclerosis was superimposed upon extensive pyelonephritis and uremia was probably the result of the combination of the two conditions.

Glomerulonephritis was the predominating renal lesion in five cases. Four of these patients were in the nephrotic stage and did not present the findings of the malignant phase of hypertension at death. The kidneys presented diffuse subacute glomerulonephritis and only minimal arteriolar and glomerular necrosis. In fact, the latter lesions were missed on the first examinations of the microscopic sections. Careful search, however, has revealed these lesions in every one of the 21 cases of the secondary group. The one patient with glomerulonephritis who had no evidence of nephrosis but in whom clinical features of the malignant phase of hypertension were revealed at time of death is of interest, since the kidneys at autopsy presented chronic lobular and sclerosing glomerulonephritis. This is the rare condition which Allen [7] believes is related to so-called "lipoid nephrosis." In this case there was also superimposed malignant nephrosclerosis.

The one patient with extensive "benign" vascular nephrosclerosis and very few necrotic arterioles died of cerebral softening. There was extensive scarring of renal tissue. The last known value of the blood urea nitrogen was 52 mg. per 100 cc., determined 13 days before death.

COMMENT

In recent reports the change in usage of the term periarteritis nodosa over a period of eight decades has been discussed,[1] and the various procedures which have been employed to produce the lesions experimentally have been described.[8] Medical literature now contains over 500 case reports under the title of periarteritis nodosa or one of its synonyms. Among these are many typical examples of each of the five categories of necrotizing angiitides outlined in Table 1. Nevertheless, our attempt to classify all of the reported cases has proved futile, since in many instances essential data for accurate classification are lacking.

Most of the cases reported as periarteritis nodosa before 1900 were typical examples of the primary type as described by Kussmaul and Maier.[4] There were gross nodules on muscular type arteries, widespread in the body except that the pulmonary vessels were not involved. These cases were reviewed in 1892 by

6. Goldblatt, H., and Kahn, J. R.: Studies on Experimental Hypertension: Experimental Observations on the Malignant Phase of Essential Hypertension; The Production of Intrarenal and Extrarenal Arteriolar Necrosis and Necrotizing Arteriolitis, Publication No. 13, American Associaton for the Advancement of Science, 1940, pp. 266-273.

7. Allen, A. C.: The Kidney: Medical and Surgical Conditions, New York, Grune and Stratton, Inc., 1951.

8. Zeek, P. M.: Periarteritis Nodosa and Other Forms of Necrotizing Angiitis, New England J. Med. **248**:764-772, 1953.

Fletcher [9] and in 1894 by von Kahlden.[10] The comprehensive reviews of the subject by Boyd included 395 case reports. These appeared in the literature between the years 1938 [11] and 1944.[5a] They included examples of each of the various types of lesions described in the present report.

Cases of secondary periarteritis nodosa are somewhat difficult to locate in the literature, because they are usually listed under the name of the underlying renal disease. In 1933 Otani [12] presented two cases of malignant nephrosclerosis in which there was periarteritis nodosa in other viscera. That same year a case of "necrotizing angiitis" associated with glomerulonephritis was reported by Helpern and Trubek.[13] In one of the cases of malignant hypertension in a child, described by Zuelzer [14] in 1951, there also was periarteritis nodosa. Other cases which fulfil our criteria for secondary periarteritis nodosa are included in Boyd's review [15] of the renal manifestations associated with periarteritis nodosa (1941).

One of the first reports describing a case of probable hypersensitivity angiitis was that of Ophüls [5b] in 1923. He listed 10 outstanding features of his case which differentiated it from the majority of the other cases of periarteritis nodosa previously reported. Between the years 1942 and 1950 many cases of hypersensitivity angiitis were reported. Most of these were associated with sulfonamide therapy,[16] but identical vascular lesions appeared to be caused by other antigens. Peale and his co-workers [17] described them in a case of scarlet fever. Typical lesions of hypersensitivity angiitis were described, by Van Wyk and Hoffman,[18] in association with

9. Fletcher, H. M.: Über die sogenannte Periarteriitis nodosa, Beitr. Path. Anat. **11**: 323-343, 1892.

10. von Kahlden, C.: Über Periarteriitis nodosa, Beitr. path. Anat. **15**:581-601, 1894.

11. Boyd, L. J.: The Clinical Aspects of Periarteritis Nodosa, Bull. New York M. Coll. **1**:219-225, 1938.

12. Otani, S.: Malignant Nephrosclerosis and Periarteritis Nodosa, Society Transactions, Arch. Path. **16**:435, 1933.

13. Helpern, M., and Trubek, M.: Necrotizing Arteritis and Subacute Glomerulonephritis in Gonococcic Endocarditis: Toxic Origin of Periarteritis Nodosa, Arch. Path. **15**:35-50, 1933.

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dilantin therapy and, by McCormick,[19] following the administration of propylthiouracil. In 1950 Wainwright and Davson [20] described necrotizing glomerulitis in association with "the microscopic form of periarteritis nodosa," a combination of lesions frequently seen in hypersensitivity angiitis.

Although no clues were apparent to us to throw light on the etiology of periarteritis nodosa, the high incidence of established hypertension in periarteritis nodosa indicates a significant association of the two conditions. A possible relationship between classic periarteritis nodosa and hypertension has been discussed from time to time in the medical literature.[21] It was first suggested by Meyer, in 1878,[22] before modern methods of measuring blood pressure were available. Of particular interest is the development of periarteritis nodosa in the course of malignant nephrosclerosis. Although this type of renal disorder was far more common than any other type of primary renal disease in our group of cases of secondary periarteritis nodosa, it was of such minimal and terminal character in six cases (Table 4) that it would not seem to be a necessary factor in the pathogenesis of secondary periarteritis nodosa. In a long-term study on hypertension, still in progress, the pathological material in 70 cases of malignant hypertension has been examined by one of us (P. M. Z.). Although arteriolar necrosis was present to some degree in every case, periarteritis nodosa was found in only 15 (21%). Furthermore, in the present study in none of the cases designated primary periarteritis nodosa was there malignant hypertension at the time of death. These observations indicate that though malignant hypertension and periarteritis nodosa occur together with significant frequency, the necrotizing vascular lesions of the two conditions are distinctly separate pathological entities and neither condition is a necessary factor in the pathogenesis of the other. Rather, it may be that there is a common etiological background.

The division of the necrotizing angiitides into the categories herein defined has proved to be far more satisfactory than trying to deal with them as manifestations of one disease entity. It is nonetheless granted that in rare cases there may be combinations of lesions and that a single biopsy section may be equivocal in regard to the differential diagnosis. When adequate sections are available, the over-all findings are distinctly different in the various types of necrotizing angiitis. With the development of newer therapeutic agents, it may become increasingly important to differentiate between categories. For example, there is evidence that corticotropin is detrimental in the course of periarteritis nodosa [23] but that cortisone may be beneficial to patients in whom there is evidence of hypersensitivity.[24]

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SUMMARY

Thirty-five cases of periarteritis nodosa and 10 cases of hypersensitivity angiitis are reviewed and tabulated. Certain striking differences in course and symptomatology have been revealed. Moreover, it has been found that cases of periarteritis nodosa are divisible clinically into two groups, which have been designated primary and secondary periarteritis nodosa.

In the 14 cases designated primary periarteritis nodosa there were widespread lesions in various stages at necropsy, after a long clinical course characterized by gastroenteric symptoms, peripheral neuropathy, hypertension usually, and eosinophilia occasionally. Twenty-one cases of secondary periarteritis nodosa were essentially cases of renal disease with hypertension, in which a few lesions of periarteritis nodosa had been initiated a short time before death. In these the clinical findings of periarteritis nodosa were masked by those of severe renal disease and hypertension.

In sharp contrast, in the 10 cases of hypersensitivity angiitis the clinical manifestations were of a fulminating disease characterized by fever, skin rash, nephritis, myocarditis, and frequently a history of recent sulfonamide ingestion.

It is concluded that periarteritis nodosa and hypersensitivity angiitis can be differentiated clinically and represent two distinct disease conditions.

HAMMAN-RICH SYNDROME

Analysis of Current Concepts and Report of Three Precipitous Deaths Following Cortisone and Corticotropin (ACTH) Withdrawal

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DIFFUSE interstitial pulmonary fibrosis of the type originally described by Hamman and Rich [1] remains a most perplexing process, which, despite its striking histological appearance, may well represent a reaction peculiar not to one but to several inciting factors. Obscure in etiology and supposedly rare in occurrence, this syndrome is nevertheless so conspicuous by the extent of pulmonary involvement, so vicious in its relentless, usually unresponsive course, and so often fatal in its outcome that it is not surprising to note the current display of interest in the subject, as a growing number of case reports and a recent editorial in *The Journal of the American Medical Association* attest. [2]

Contrary to an erroneous concept being perpetuated in the literature, the original paper by Hamman and Rich appeared not in 1944 but in 1935.[1] Fully nine years elapsed before they published what has come to be regarded as the classic description of the disease,[3] wherein they presented a more detailed discussion and added a fourth case report to their previous three. Over the ensuing years, 14 deaths due to an essentially similar process have been reported,[4] including the "living

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(Footnote continued on next page)

twin" of Peabody and co-workers [4d] who has subsequently been autopsied and the diagnosis confirmed.[5] Thus the list of authentic cases, including the 3 in this report, numbers only 21.

This figure does not include several cases accepted in other reviews,[4j,k] which we have tentatively rejected on the grounds that each resembled in some particular detail one of the collagen diseases in which pulmonary fibrosis not infrequently occurs. The case of Kneeland and Smetana,[6] for example, manifested in the pulmonary arterioles lesions compatible with periarteritis nodosa, while that of Katz and Auerbach [7] showed contracture deformities and atrophy of the hands resembling scleroderma or dermatomyositis. Because of peculiar retinal cytoid bodies and intra-alveolar organization, Tumulty's three patients [8] are also placed in this group. We admit, however, that time and further study may show the exclusion of these cases to be unjustified.

Few though the reported cases may be, there is reason to believe that the disease is by no means as rare as the literature would indicate. In papers by Spain,[9] Humphreys,[10] and Rubin and co-workers [4i] casual reference is made to a total of 10 potential instances of the disease, but the descriptions are too meager to substantiate their exact identity. Geever and co-workers [11] have demonstrated the same histological picture confined to a single lobe, and it may well be that localized and nonfatal forms of the disease occur. Scadding [12] makes mention of a case showing some similarity to this syndrome, in which he felt that the chronicity of the process invalidated the diagnosis. In personal communications we have learned of other unreported cases, Dr. Louis Siltzbach, of New York, having encountered three; Dr. Sol Katz, of Washington, D. C., two, and Dr. Robert L. Breckenridge, of Philadelphia, still another. One of us (J.W.P.) has collaborated in the report of an additional case now awaiting publication.[13] In all likelihood time will prove that the disease is uncommon but not rare.

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At our present stage of understanding, it is impossible either to confirm or to deny any of the various factors proposed as the cause of the disease. Perhaps the most attractive hypothesis is that which proposes a viral origin, but such a conclusion stems more from the lack of evidence to support a bacterial or occupational etiology than from any positive evidence in its favor. Thus, inclusion bodies have not been demonstrated, and a virus has never been isolated. It is true, however, that occasional cases of primary atypical pneumonia will in some areas bear a resemblance to the Hamman-Rich syndrome,[14] and in protracted or recurrent cases of influenza somewhat similar histological changes are encountered. Therefore, its emergence from a variant form of these viral infections is a distinct possibility. Moreover, the tremendous degree of hypertrophy and metaplasia which characterizes the alveolar lining cells in this disease is not completely dissimilar from that of pulmonary adenomatosis, a disease thought by some investigators to be of viral etiology on the basis of successful transmission experiments in a closely akin condition, epizootic adenomatosis of sheep (jaagsiekte). Nevertheless, all of these conditions generally present distinct histological differences, chief among which is the absence of a widespread and progressive fibroblastic proliferation. Long ago it was shown[15] that a marked hyperplasia of the alveolar lining cells could be produced by intrapleural injection of any one of many irritating solutions, thus indicating the nonspecificity of this feature alone.

Then again, the Hamman-Rich syndrome may represent a collagen disease localized to the lungs. Rheumatic pneumonia presents some histological similarity, as do some cases of antigenic pneumonitis,[16] but the over-all picture is far from identical. Scleroderma is often associated with a diffuse interstitial fibrosis of the lungs, but, aside from the deposition of collagen, reported cases have shown little to suggest a relationship to the interstitial fibrosis of Hamman and Rich. Breckenridge,[17] however, has noted practically the same histological changes in several cases of scleroderma and regards as highly probable the possibility of the Hamman-Rich syndrome being a collagen disease. While such speculation is interesting and may eventually prove true, inferences as to etiology based on partial similarities are at present unjustified. The genetic implications of its occurrence in identical twins[4d] are also fascinating but not particularly informative. Chronic pulmonary lymphedema has been suggested as an etiological factor,[4k] but, even if it be so, it hardly serves to clarify the issue. If, as some suggest, the disease is increasing, this may point to some sort of air pollution coincident to modern industry, but this and other vague proposals, such as an unknown fungus, hyperergy, etc., can hardly be regarded as anything more than the gropings of our collectively bewildered mind, and ultimately we find ourselves obliged to admit that the cause or causes of the Hamman-Rich syndrome are, for the present at least, unknown.

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As we have gained additional experience with this disease it has become increasingly obvious that the term acute diffuse interstitial fibrosis of the lungs is both inaccurate and cumbersome. Various reports [18] have established the existence of chronic forms of the disease. Moreover, since the word fibrosis refers solely to the pathological end-result, it would probably be preferable to supplant the older terminology with the designation, "diffuse fibrosing interstitial pneumonitis," as suggested by Cox and Kohl [4] and further supported by the dramatic response to cortisone in Case 1 below. Once again, however, such a term would be just as unwieldy and therefore equally undesirable. More concise appellations, such as cirrhosis of the lung and idiopathic pulmonary fibrosis, also have obvious shortcomings, the worst of which is a complete lack of specificity. For these reasons, we have become accustomed to refer to these cases as the Hamman-Rich syndrome, preferring to call it a syndrome rather than a disease because of some uncertainty as to the common origin of these cases. We note that in a recent publication an English authority intimates a preference for the same terminology.[12] In general usage this term has proved popular, has never suffered from confusion with Hamman's syndrome (spontaneous mediastinal emphysema), and should provide a preciseness of meaning which those only vaguely familiar with the condition could not appreciate in the older phraseology.

The Hamman-Rich syndrome is best defined as an acute or chronic pulmonary disease of unknown etiology characterized clinically by cough, dyspnea, and cyanosis in association with minimal physical findings and a progressive, essentially afebrile course; radiographically by parenchymal and hilar densities, the only definitive characteristic of which is the eventual tendency toward diffuse bilateral involvement, and pathologically by an extensive fibrosis as well as a round-cell and plasma-cell infiltration confined to the interstitial tissue of the lung. Of critical importance are the absence of a significant acute inflammatory response and the inability to demonstrate an acceptable etiologic factor despite an intensive diagnostic investigation.

Dyspnea and cyanosis dominate the clinical picture, and a dry paroxysmal cough is a frequent complaint. Inconstant clinical findings include sore throat, chest pain, hemoptysis, weight loss, and clubbing of the digits. Almost one-half these patients show some degree of cor pulmonale. The progress of the disease may be fulminating, with death within a few weeks after the onset of symptoms, while in other instances, except for intermittent exacerbations probably associated with secondary infection, the decline is almost imperceptible and may extend over many years. In both forms of the disease the patient gradually reaches the point of cyanosis even at rest and eventually dies of respiratory insufficiency. Because of the borderline pulmonary reserve which these patients manifest, a relatively mild respiratory infection may prove rapidly fatal. Fever and leucocytosis appear usually for the first time in the terminal stages. An elevation of the sedimentation rate is often noted and polycythemia may occur in the more chronic cases,[19] but on the whole laboratory studies are inconclusive.

The roentgenologic appearance conforms to no set pattern. Initially it may consist of peritruncal accentuation in conjunction with hazy or patchy densities, which commence more often in the pulmonary bases and gradually spread throughout the lungs. On the other hand, a diffuse mottled appearance may exist from

18. Footnote 4*d*, *e*, *f*, *h*, and *i*.

19. Footnote 4*c*, *d*, and *e*.

the outset, being comprised of a reticular network with a superimposed granular or nodular pattern which in the late and terminal stages may show a tendency toward coalescence. Accentuation of the hilar and vascular markings and mediastinal widening are fairly typical but are not necessarily distinctive. Small pleural effusions occasionally occur. On the basis of roentgenologic findings alone, it is impossible to differentiate this syndrome from any of the innumerable diseases capable of producing diffuse reticular or nodular shadows.

When the above picture is encountered, the diagnosis may certainly be suspected, but we cannot accept without qualification the statement by Callahan and co-workers [4k] that the "roentgenographic findings associated with the symptoms of cough, hemoptysis and dyspnea with progressing cyanosis are sufficient to establish a clinical diagnosis." The problems inherent in the differential diagnosis of diffuse pulmonary lesions are among the most complex and the most exasperating that one can experience. The diseases which can mimic the Hamman-Rich syndrome are quite numerous and include miliary tuberculosis, diffuse chronic productive pulmonary tuberculosis, atypical pneumonia, some of the pulmonary mycoses, sarcoidosis, berylliosis, silicosis, asbestosis, bagassosis, lymphangitic carcinomatosis, pulmonary adenomatosis, leukemic infiltration of the lung, and pulmonary fibrosis secondary to Hand-Schüller-Christian disease and the collagen diseases. Thus, the clinical diagnosis of the Hamman-Rich syndrome is based primarily on a process of exclusion; consequently it cannot justifiably be made until the most exhaustive work-up has failed to detect a significant etiologic factor. Even then such a conclusion would appear hazardous although inviting.

In the final analysis, the diagnosis can be established only by a study of pulmonary tissue obtained by lung biopsy or at autopsy. Grossly the lungs may be described as firm, solid, rubbery, noncollapsible, heavy, livery, carnified, or cirrhotic-looking. The pleural surfaces are usually spared. Crepitation is markedly diminished or absent, and the lungs usually sink when placed in water. Emphysematous changes are for the most part inconspicuous. On cut surface the lungs present a dry granular fibrotic texture, with a lacy network extending throughout the parenchyma. On some occasions the fibrotic nature of the process may be masked by pulmonary edema. The tracheobronchial tree is characteristically devoid of purulent exudate, but a moderate tracheobronchial lymphadenopathy is not uncommon.

By far the most distinctive feature of the disease is its microscopic appearance. The pulmonary interstitial tissue is everywhere pervaded by a profuse fibrous reaction varying from a vigorous proliferation of young fibroblasts to the deposition of large quantities of hyalinized connective tissue. Intermingled with the fibrous elements can be seen numerous chronic inflammatory cells, consisting predominantly of lymphocytes and plasma cells, with a few macrophages and occasionally a significant number of eosinophiles.[20] Polymorphonuclear leucocytes can always be found but are seldom prominent. Rare multinucleated giant cells are seen. They usually have the nonspecific appearance of foreign body giant cells, but some believe that they arise by fusion of adjacent fibroblasts rather than from the presence of a specific irritant.[4k] Due to the massive interstitial infiltration with young granulation tissue, collagen, chronic inflammatory cells, and occasional lymphoid follicles, the alveolar septa are widened, sometimes to a degree sufficient to encroach upon

20. Hamman and Rich.[1] Hamman and Rich.[3]

and obliterate many alveoli. The alveolar walls are themselves markedly thickened and lined with sheets of cuboidal cells, which have been interpreted by some as alveolar phagocytes and by others as metaplastic alveolar epithelial cells. Sheets of these cells may fill the alveoli and occasionally impart a peculiar pseudoglandular appearance.[4b,l]

Characteristically the alveolar spaces are remarkably free of purulent exudate but may contain round cells and exfoliated masses of alveolar lining cells in a thin fibrinous exudate. The extraordinary amount of fibrinous exudate exhibited in the case of Callahan and co-workers,[4k] coming as it has at the height of interest in this disease, has created a false impression that this finding is essential to the histological diagnosis. Actually it is the first instance in which such a response has so dominated the picture. Ordinarily very few if any areas show organization of the intra-alveolar exudate such as one commonly sees with the various chronic organizing pneumonitides. Fat-filled macrophages may be found within the alveolar lumina and interstitial tissue, the lipoid material presumably being of endogenous origin as a result of tissue breakdown. In several cases fat stains have been positive.[21]

The peribronchial and perivascular spaces, like other portions of the interstitial tissue, show varying amounts of fibrosis. Squamous metaplasia of the bronchiolar epithelium is sometimes quite prominent, and the bronchiolar lumina may contain some purulent exudate as a result of terminal bacterial invasion. Because pulmonary hypertension is a natural consequence of diffuse interstitial fibrosis, the pulmonary arterioles not infrequently show subintimal proliferation. Reticuloendothelial hyperplasia of the tracheobronchial and mediastinal lymph nodes is not unusual.

In every instance to date this disease has remained singularly unresponsive to all forms of therapy. Except for the administration of oxygen and symptomatic care there is little the physician can do for these patients. Because of the favorable response to cortisone and corticotropin (ACTH) therapy manifested by a number of diffuse pulmonary granulomatoses, notably sarcoidosis and berylliosis, hope had also been held for a similar beneficial effect in the Hamman-Rich syndrome. However, in those reported cases in which these hormones have so far been utilized,[22] the results have been consistently disappointing. Despite the fact that we have now witnessed for the first time a most dramatic demonstration of the potential value of cortisone and corticotropin in the management of this disease, we remain ever so much more impressed with the limitations and dangers of hormonal therapy. It is with this aspect of the problem that this report is primarily concerned.

Although we intend in no way to minimize the amply authenticated risk of reactivating dormant tuberculous foci coincidental to cortisone and corticotropin therapy, it is nevertheless true that the concomitant administration of streptomycin has provided a seemingly effective measure in precluding most complications of this sort. A hitherto unpublicized but equally dire hazard attending the use of cortisone and corticotropin in the presence of diffuse indeterminate pulmonary pathology is exemplified by the three patients in this report, in all of whom a violent exacerbation of their pulmonary disease developed, in two after withdrawal of cortisone and in the other after a decrease in corticotropin dosage. That this complication proved fatal on all three occasions illustrates the seriousness of the problem and has prompted us to bring it to the attention of the profession.

21. Rubin, Kahn, and Pecker.[41] Knee'and and Smetana.[6] Peabody and Peabody.[13]

22. Footnote 4*i*, *j*, and *k*.

REPORT OF CASES

CASE 1.—J. L. P.,[23] a 31-year-old white farmer, was admitted to the hospital on Oct. 12, 1952, with a history of cough, progressive dyspnea, fever, and chest pain of three months' duration, which had not responded to vigorous antibiotic therapy. Past history, including exposure to noxious inhalants, was negative. Except for tachypnea and slight cyanosis physical examination was not remarkable. A persistent hyperglobulinemia (globulin ranging from 3.7 to 4.2 gm. per 100 cc.) was noted, but other laboratory studies, including tuberculin, coccidioidin, histoplasmin, and blastomycin skin tests, were all negative. Hemolytic Staphylococcus aureus was repeatedly isolated from the sputum, but repeated smears and cultures for other pyogens, acid-fast bacilli, and fungi were unrewarding. Sputum examinations for malignant cells were also negative.

A routine posteroanterior roentgenogram of the chest disclosed bilateral diffuse finely nodular mottled densities, which appeared to follow the pulmonary vascular pattern and fanned outward from the hilar areas throughout the major portions of both lungs (Fig. 1). X-rays of the hands, feet, and skull showed no abnormalities.

Administration of alternate courses of penicillin and streptomycin, oxytetracycline (Terramycin), chloramphenicol, and erythromycin had no apparent effect on the severity of the disease. When a thorough diagnostic investigation, including biopsies of two lymph nodes, liver, sternal marrow, and muscle, failed to establish a specific etiologic diagnosis, a course of corticotropin was instituted as a desperation measure under streptomycin protection. Initial dosage was 15 units daily administered intravenously over an eight-hour period. Within several days considerable subjective improvement was noted, whereupon the dosage was decreased to 10 units daily. Chest roentgenograms taken 5 and 13 days after the institution of corticotropin therapy disclosed a remarkable clearing of both lung fields, with the persistence only of a fine reticular pattern. Except for a brief clinical recrudescence following an unsuccessful attempt to switch to the corticotropin gel, a prolonged remission was maintained even though cortisone by mouth, 100 mg. daily, was substituted.

During one month of cortisone therapy the patient remained essentially symptom free, gained 20 lb. (9 kg.), and attained a fairly normal state of activity. Over this same period cortisone therapy was gradually terminated by successive decrements in dosage. For the seven days prior to and four days following complete cessation of cortisone therapy, corticotropin was briefly reinstituted in small doses.

Quite suddenly, on the fifth day following cessation of corticotropin and nine days after the termination of cortisone therapy, the patient became extremely dyspneic and cyanotic. A chest roentgenogram at this time revealed a complete return to the initial picture, with a tendency toward confluency of the diffuse nodular pattern. Despite reinstitution of massive corticotropin and cortisone therapy, fulminating respiratory insufficiency developed and the patient died within 24 hours. The entire clinical course, from onset of symptoms to death, on Jan. 14, 1953, lasted only five and one-half months.

Autopsy (Dr. W. B. Sorrell).—Significant findings at autopsy were limited to the lungs and lymph nodes. The combined weight of the lungs was 1,675 gm. The pleural surfaces were smooth and glistening. In consistency the lungs were firm and rubbery throughout all lobes. There was no crepitation, and when placed in water the lungs promptly sank. On section they presented a uniformly gray granular appearance with a glazed surface. A fine fibrous network could be discerned upon close inspection. The tracheobronchial tree was free of exudate. There was a most remarkable and widespread hyperplasia of the lymph nodes, extending paravertebrally from the second thoracic to the first sacral vertebra, with involvement also of the tracheobronchial and paratracheal nodes, the nodes in the mesentery of the small bowel, and those along the spenic, external iliac, and femoral arteries, some of which measured 2 to 3 cm. in diameter. On cut surface they presented a gray lymphoid appearance. It was the opinion of some examiners that the right ventricle was slightly dilated, but the ventricular walls were not hypertrophied. The adrenal glands presented a normal appearance, with the usual ratio of cortex to medulla. Multiple cultures were taken from lungs and lymph nodes, but no growth was observed on blood agar, Sabouraud's agar, and Petragnani's medium.

23. To be reported in detail by Dr. M. M. Schecter.

Microscopic Examination: Sections from all lobes showed a similar picture (Fig. 2). The pleura was slightly thickened but was not otherwise remarkable. The interstitial tissue throughout the full extent of both lungs presented a profuse infiltration with lymphocytes, plasma cells,

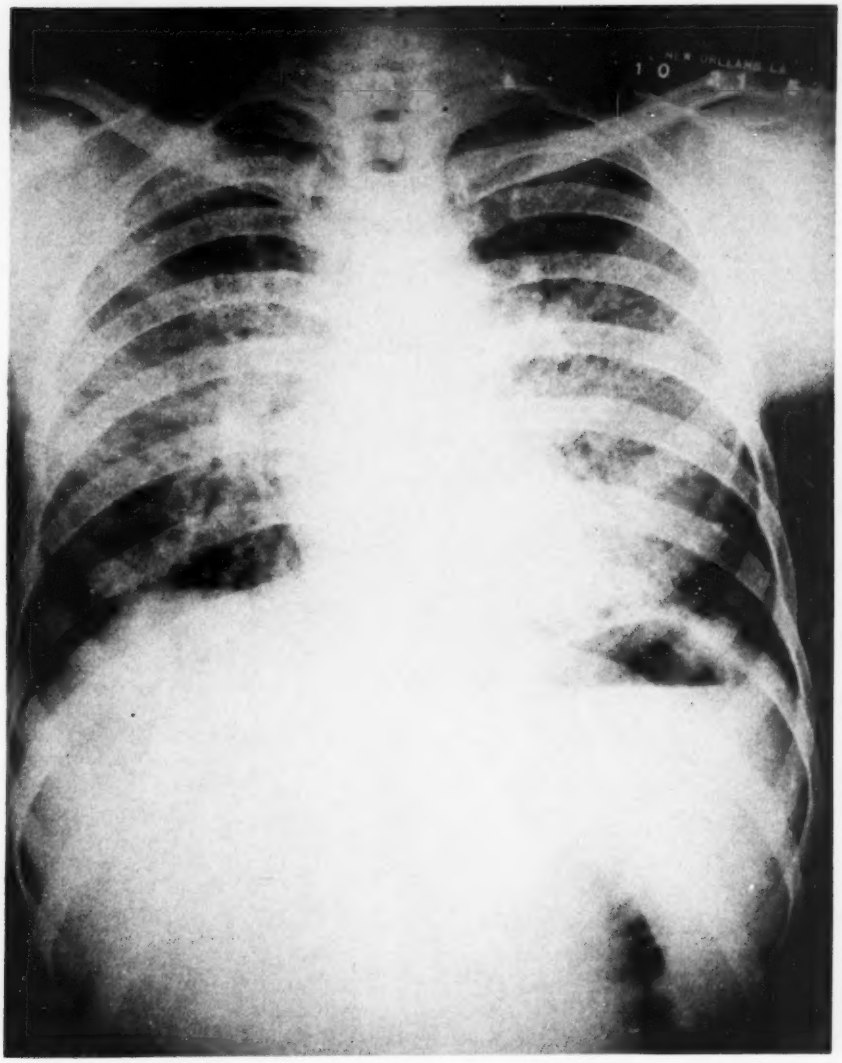

Fig. 1 (Case 1).—Posteroanterior roentgenogram showing diffuse, finely nodular densities throughout both lungs. Remarkable clearing followed corticotropin therapy, but after cortisone and corticotropin withdrawal there was a return of the extensive roentgenographic changes, with a tendency toward confluency.

macrophages, and occasional neutrophiles. Numerous dilated capillaries were noted. In some areas the process appeared to be of quite recent origin, while in others it was of longer duration, as manifested by the deposition of collagen. So thickened were the alveolar septa in certain areas

that the alveoli were greatly distorted and in part obliterated. The alveolar lining cells exhibited cuboidal metaplasia of a prominent degree throughout all sections. The alveoli on the whole were remarkably free of exudate, but in some areas they contained an eosinophilic material, with lym-

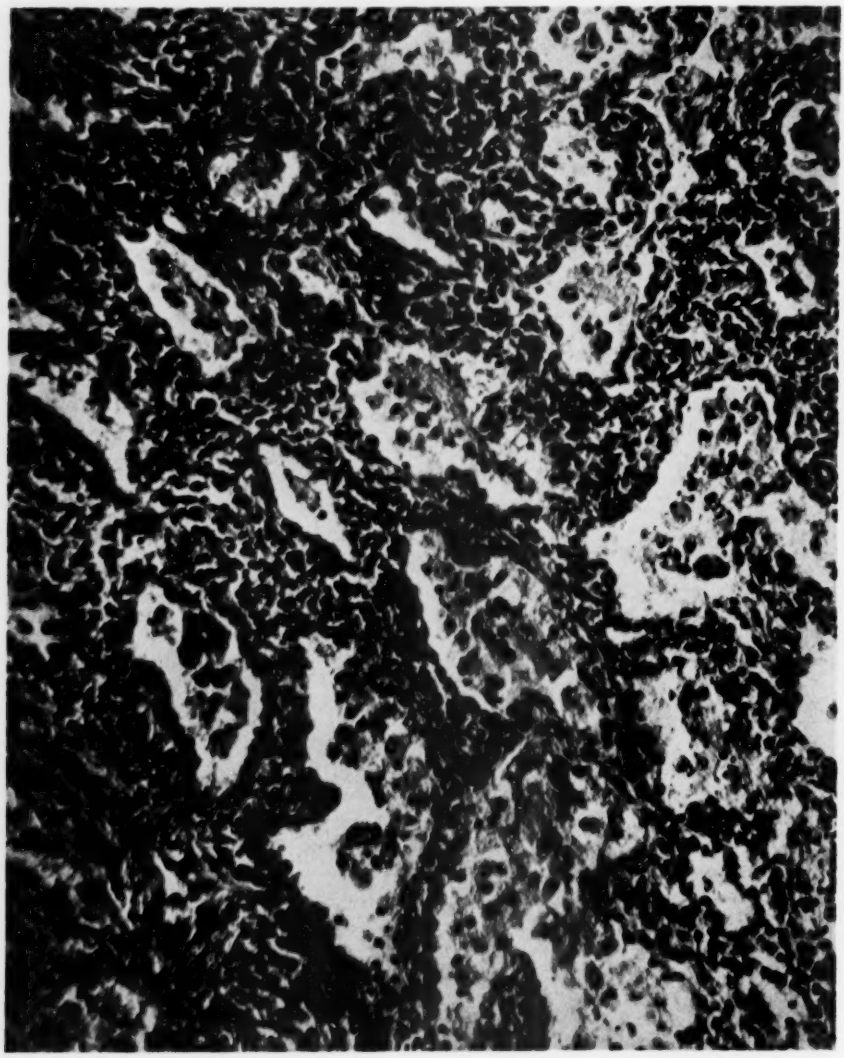

Fig. 2 (Case 1).—Representative microscopic section of lung demonstrating the pronounced round cell infiltration, fibroblastic proliferation, and alveolar lining cell metaplasia which characterized this fulminating example of the Hamman-Rich syndrome.

phocytes, plasma cells and macrophages. Clumps of desquamated alveolar lining cells filled some of the lumina, and an occasional alveolus was lined by a hyaline membrane. Very few polymorphonuclear leucocytes could be found in the alveoli, but in the bronchioles and bronchiolar walls a slight purulent response was noted. Nonspecific nodular foci of epithelioid cells and an occasional

foreign body type giant cell were scattered throughout the alveolar septa. Gram, Giemsa, acid-fast, and Hotchkiss-McManus stains revealed no organisms. The lymph nodes showed marked reticuloendothelial hyperplasia, with a moderate increase in plasma cells. No abnormalities were noted in either adrenal gland.

Fig. 3 (Case 2).—Lung section from a more chronic case, in which is seen an essentially similar picture except for a more marked deposition of fibrous elements.

CASE 2.—M. R., a 72-year-old white woman, first began to experience a bothersome but unproductive cough in October 1950, at which time the only abnormal physical finding was the presence of fine left basilar rales. Except for angina on effort, she had no other complaints until January 1952, when she became increasingly incapacitated by violent paroxysms of coughing. At the time, because of radiographic evidence of a diffuse interstitial pulmonary infiltration,

she was studied rather extensively elsewhere without the detection of any etiological leads. Bronchoscopy in July 1952 was not remarkable, and bronchoscopic washings, which afforded the first sputum ever raised, were also negative by smear and culture for acid-fast bacilli, fungi, and other pathogens.

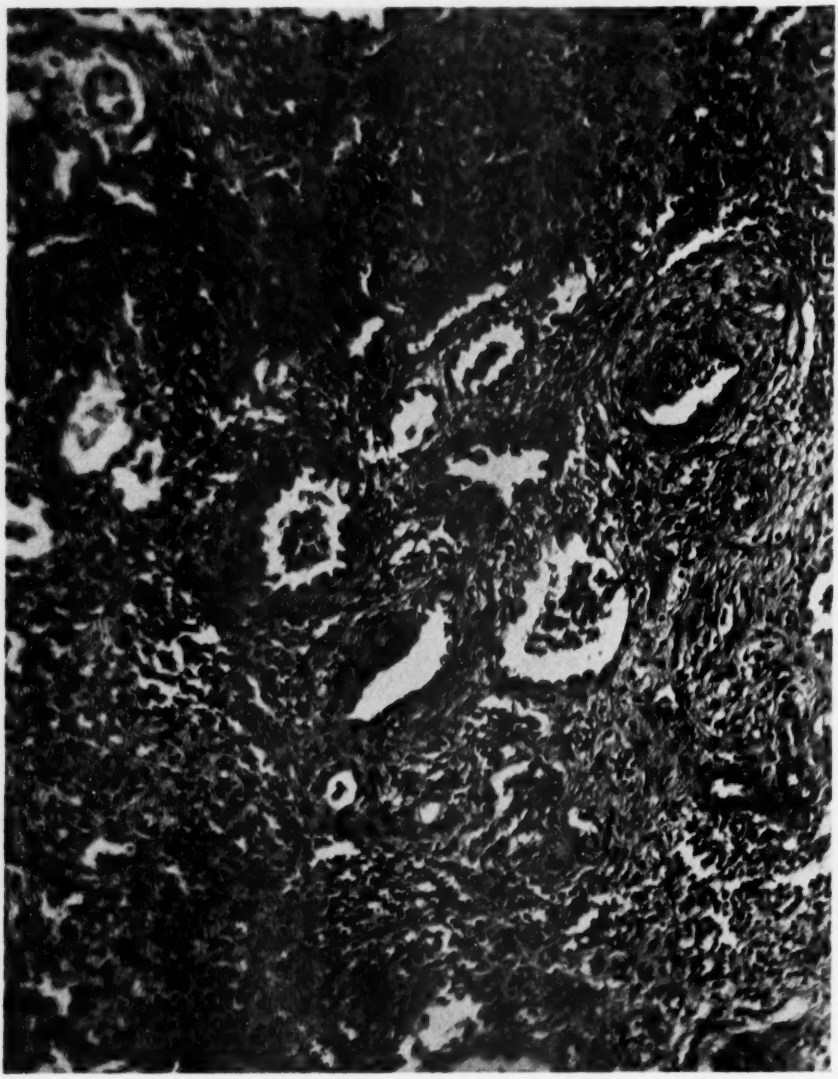

Fig. 4 (Case 3).—Microscopic section from the lung biopsy showing the far-advanced degree of interstitial fibrosis encountered eight years after onset of symptoms.

When seen in June 1952, roentgenograms of the chest disclosed a diffuse coarsely reticular infiltration disseminated throughout both lung fields (Fig. 5). In some areas the reticular network was broken up into finely nodular densities, which appeared more prominent in the upper one-half of the right lung. The patient was still experiencing no dyspnea except after

paroxysms of coughing, but this was attributable in part to the severely restricted activity enforced by her angina. The cough continued to be completely nonproductive, although gradually increasing in severity. The patient was and had always been essentially afebrile. Inhalational

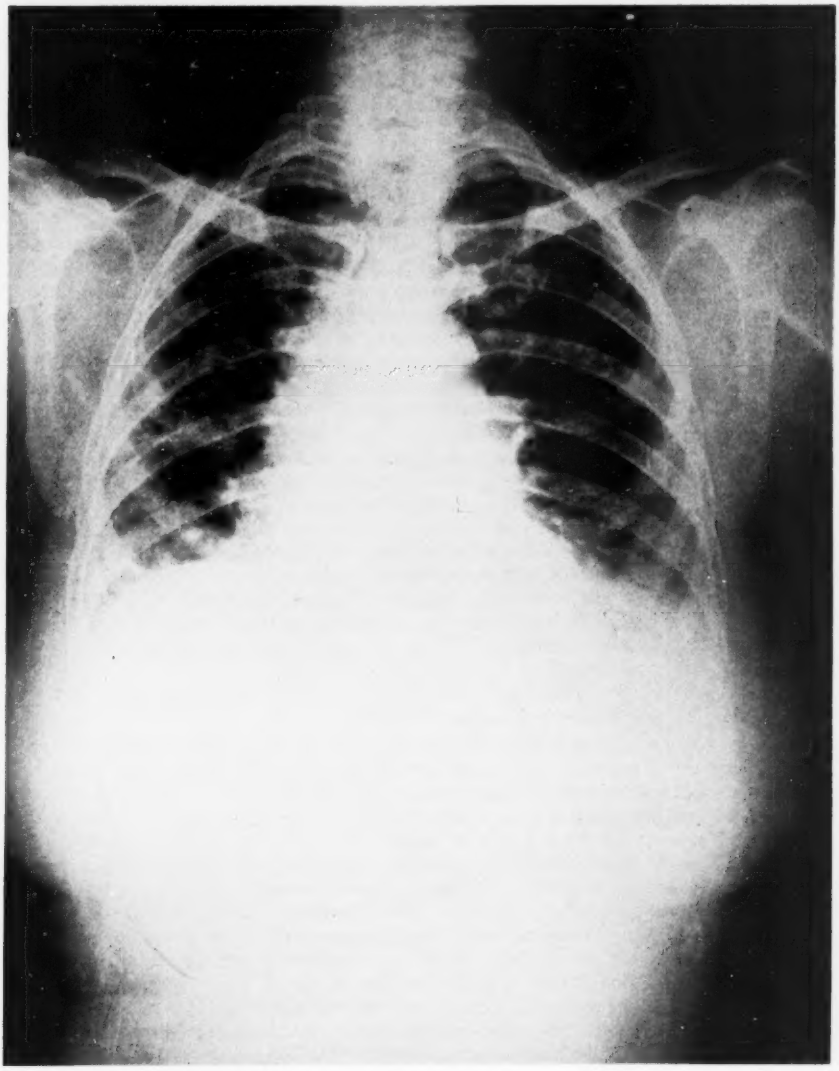

Fig. 5 (Case 2).—Posteroanterior x-ray showing diffuse coarsely reticular densities disseminated throughout both lung fields.

exposures of any sort were denied, and the remainder of her history was in no way remarkable. Results of multiple laboratory studies were either negative or normal. Tuberculin, histoplasmin, and coccidioidin skin tests were negative.

A diagnosis of sarcoidosis was then proposed, and, because of obvious progression of her disease, the patient received a course of cortisone, 75 mg. daily, over a three-week period

extending from Oct. 6 to 26, 1952, with the concomitant administration of dihydrostreptomycin, 1 gm. daily five times a week. Although slight subjective improvement was claimed by the patient, no roentgenographic improvement could be detected.

Cortisone therapy was then stopped abruptly. Seven days after its cessation the patient noticed that her cough became more intense and for the first time she displayed a low-grade fever. Thereafter her condition declined rapidly, and within a week she was dyspneic, orthopneic, and cyanotic at rest. Because of increasingly severe substernal pain, an electrocardiogram was obtained and disclosed a slight inversion of T waves in Lead III and in all of the precordial leads. One week after the development of severe pulmonary distress, the patient died of what can best be termed asphyxia. The clinical course from onset of symptoms to death covered 25 months.

Autopsy (Dr. A. J. Hertzog).—Significant findings were limited to the respiratory tract. Each pleural space contained several hundred cubic centimeters of clear serous fluid. The pleural surfaces were smooth, glistening, and free of adhesions. The right lung weighed 500 gm., the left, 600 gm. The lungs were firm and did not collapse. The lung surfaces presented numerous small pale raised areas which by palpation were demonstrated to be small emphysematous blebs. Cut surface revealed a diffuse patchy consolidation with a firm nodular appearance and reddish-brown color. The entire parenchyma appeared to be spanned by a fibrous network. There was moderate pulmonary edema, and the bronchi contained a clear frothy material but no pus. Moderate tracheobronchial and paratracheal lymph node enlargement was noted, some nodes measuring 2 cm. in diameter. The adrenal glands were not grossly remarkable. Except for the heart, where coronary sclerosis and myocardial fibrosis were encountered, the other organs were not abnormal.

Microscopic Examination: Sections from all portions of the lungs revealed a similar picture throughout (Fig. 3). The alveolar septa were markedly thickened and contained large numbers of lymphocytes and plasma cells. The amount of collagen varied from place to place, with some areas having large quantities of hyalinized fibrous connective tissue. The alveoli were decreased in number, and those which remained were often dilated and exhibited marked metaplasia of the alveolar lining cells. Hyaline membrane lined many alveoli, while others contained coagulated serum, round cells, neutrophiles, and nests of alveolar lining cells. No giant cells were noted. Gram and Hotchkiss-McManus stains failed to demonstrate any definite mycelial filaments. Acid-fast stains were also negative. The adrenal glands and other organs presented no abnormalities.

Bacteriology: Multiple cultures were taken from the lungs. Nocardia asteroides, pathogenic for chick embryos, was isolated in pure culture.

Case 3.—J. W. S., a 38-year-old white male engineer, was first seen in February 1952, with a chief complaint of severe incapacitating dyspnea associated with cough, night sweats, and weight loss, which had begun 8 years ago while he was serving with the Army in North Africa and had slowly and intermittently progressed in the interim. Past history and system review were not remarkable except for the fact that the patient had worked in an asbestos plant 12 years previously. Physical examination was essentially unrevealing. The heart presented only an accentuated pulmonic second sound. Moderate pulmonary osteoarthropathy was noted. X-Rays of the chest disclosed a striking degree of fine, evenly distributed mottling throughout both lung fields. Comparison with films taken several years previously showed a similar diffuse mottling of a less marked degree at that time. Results of a meticulous work-up were normal in all respects except for a sedimentation rate of 31 mm. per hour.

Exploratory thoracotomy revealed a "cirrhotic-appearing" lung, from which a biopsy specimen was taken. Multiple cultures were negative for pathogens. Microscopic sections were compatible with the chronic phase of the Hamman-Rich syndrome. A severe degree of interstitial fibrosis was noted, with an accompanying, but less marked, inflammatory reaction consisting of lymphocytes, plasma cells, and eosinophiles. In a few areas an early fibroblastic response comparable to that in Case 1 was seen. Minimal intra-alveolar exudate was noted, but in many alveoli a hyaline membrane could be seen. Most of the alveoli presented a pronounced cuboidal metaplasia, and the bronchioles had a slight degree of squamous metaplasia. Moderate intimal thickening of the arterioles was also noted. Nowhere was there evidence of an acute purulent component, nor were any organisms or asbestos bodies demonstrable in specially stained sections. A postoperative electrocardiogram indicated right ventricular strain. Although the patient

continued slowly to deteriorate, he refused cortisone therapy and left the hospital in May 1952, despite his inability to walk 25 yd. (22.8 meters) without resting. At that time his case was reported along with another as a probable instance of the Hamman-Rich syndrome.[13]

Following discharge he was able to hold a sedentary job, but by September 1952 his dyspnœa

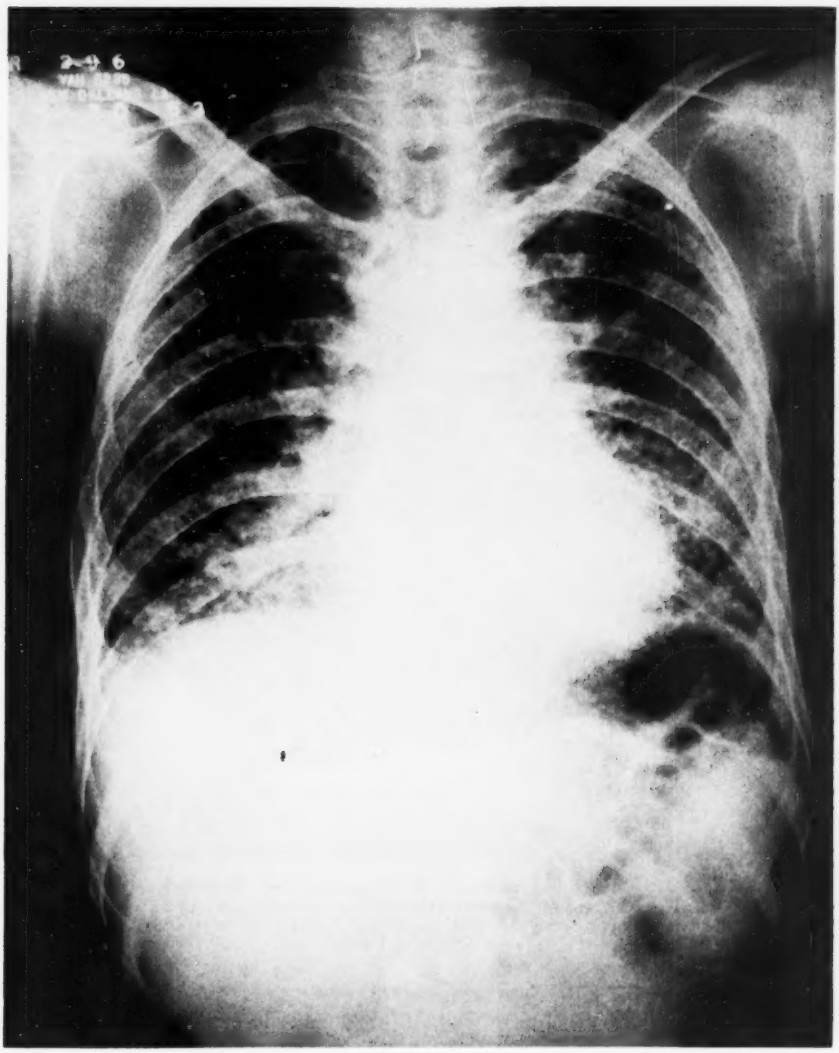

Fig. 6 (Case 3).—Posteroanterior x-ray presenting an evenly distributed, finely nodular mottling throughout both lungs.

again showed a progressive increase in severity associated with increasing productivity of cough and weight loss. He eventually returned to the hospital on Jan. 20, 1953, because of his complete incapacitation.

On readmission he was afebrile, intensely cyanotic, and markedly tachypneic, with a respiratory rate of 50 per minute. A few coarse and many fine rales were audible throughout both

entire lungs. The second pulmonic sound was louder than the second aortic sound, and the clubbing of his digits was more marked than previously. No lymphadenopathy was noted. A careful ophthalmoscopic examination revealed no "retinal cytoid bodies."[8]

Roentgenograms of the chest presented essentially the same picture as on the previous admission (Fig. 6). An electrocardiogram showed further lowering of T waves and increased right axis deviation. Sputum smears and cultures were negative for acid-fast bacilli and fungi, although Staph. aureus, alpha and beta streptococci, and Neisseria catarrhalis were recovered from one specimen. An initial white blood cell count of 11,900 progressively increased to 17,200 just prior to death. Sedimentation rate was 35 mm. per hour (Westergren). Results of other laboratory studies were not noteworthy.

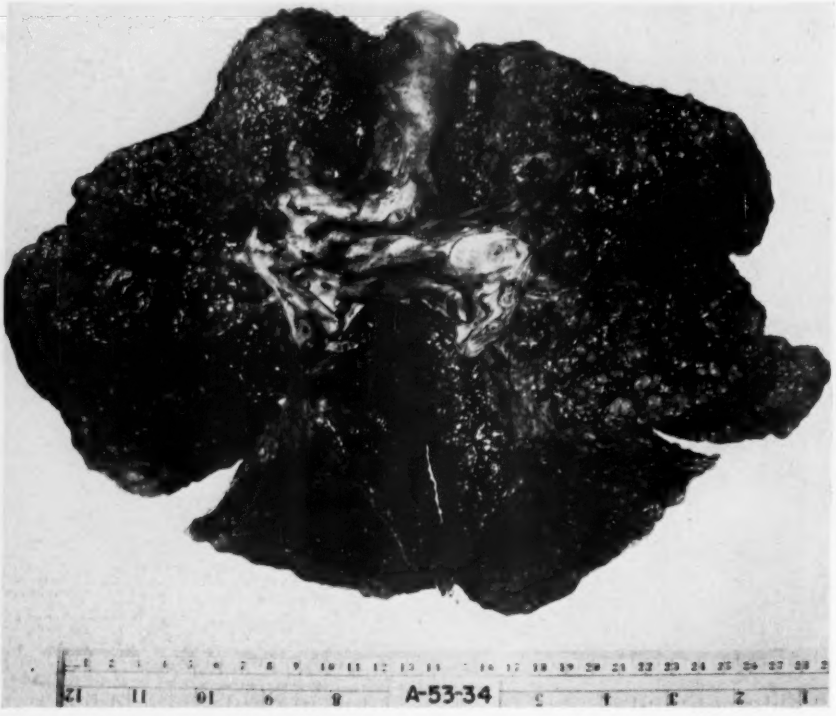

Fig. 7 (Case 3).—Photograph of the lungs, illustrating the "cirrhotic" appearance sometimes described. The scattered nodules represent small emphysematous blebs. These lungs were very firm, did not collapse, were cut with considerable resistance, and sank when placed in water.

Initial treatment utilized oxygen, penicillin, methoxyphenamine (Orthoxine), and aminophylline, and after six days on this regimen the only visible improvement consisted of diminished expectoration. Corticotropin administration was then begun in a daily dosage of 25 mg. intravenously over an eight-hour period. Ten days later no significant response had been noted; consequently the dosage was increased to 50 mg. daily and this dose was maintained for 17 days. Although the dyspnea and the diffuse infiltration seen on x-ray examination were not appreciably altered, the patient's appetite improved and he gained weight and a general sense of well-being developed.

It was then decided to decrease the corticotropin gradually and substitute a maintenance dose of cortisone, because of the obvious advantage of oral administration. Accordingly, the patient received 40 mg. of corticotropin daily for three days and then 30 mg. daily. Forty-eight hours

after the reduction of corticotropin to 30 mg. the patient became extremely dyspneic and almost black with cyanosis and coughed up large quantities of tenacious sputum. Between gasps he stated that he felt worse than at any time before in his illness. Corticotropin, 50 mg. daily, was immediately reinstituted, with 300 mg. of cortisone daily. Despite these measures the patient remained in severe respiratory distress and died March 6, 1953, eleven days after the onset of the recrudescence and nine years after his first symptoms.

Autopsy (Drs. Joseph Ziskind and Thomas G. Lyons).—The pleural cavities were free of fluid. The combined weight of the lungs was 1,400 gm. In external appearance the lungs bore a noteworthy resemblance to a shrunken cirrhotic liver (Fig. 7), for the entire surface of each lung was studded with nodules approximately 2 mm. in diameter, which by palpation were found to be minute emphysematous blebs. Both lungs were of firm consistency, did not collapse, and sank when placed in water. Crepitation was markedly diminished. A small pleural scar was present over the lingula, representing the site of previous biopsy. When sectioned the lungs were found to be quite resistant to cutting. The cut surface presented many tiny and a few large air spaces, with a dense intervening fibrous network which had obliterated the normal lung parenchyma. The tracheobronchial tree contained only a small amount of glazed tenacious exudate. The paratracheal and tracheobronchial lymph nodes were markedly enlarged, some measuring 3 cm. in diameter. These nodes were rubbery and dark gray on section.

The right ventricle was dilated, and its wall was quite enlarged, measuring up to 1.5 cm. in thickness. The left ventricle was likewise hypertrophic. The adrenal glands were within the upper limits of normal in size, with a normal ratio of cortex to medulla. Other organs showed no significant abnormalities, and multiple cultures of both lungs and lymph nodes were negative.

Microscopic Examination: Sections from all lobes showed an essentially similar appearance (Fig. 3). Alveoli were greatly reduced in number owing to the deposition of massive sheets of dense fibrous tissue. The alveoli that remained were thickened and dilated, some to a tremendous degree, and were lined by low cuboidal epithelial cells. Some alveoli contained a large amount of purulent exudate, while in others many hemosiderin-filled macrophages were seen. In addition to fibrosis the interstitial tissue presented an infiltration with mononuclear cells and plasma cells, the interstitial eosinophiles being much fewer than those in the lung biopsy obtained one year previously. A few scattered nests of epithelioid cells were noted. The blood vessels were severely congested, and the arterioles showed a very marked subintimal proliferation. No fibrinoid degeneration was seen. Comparison with the lung biopsy specimen demonstrated that in the terminal phase the metaplasia of the alveoar lining cells was much less marked, while the fibrosis itself was still more diffuse and more advanced. Although there was evidence of a terminal purulent process, multiple stains of lung sections were negative for micro-organisms. No abnormalities were found in the adrenal glands.

COMMENT

Each of these patients presents a different phase of the Hamman-Rich syndrome, the first representing the acute fulminating form of the disease; the second, an intermediate type, and the third, the chronic variety. The progression of the disease from an initial stage of vigorous fibroblastic proliferation and round-cell infiltration to one of extreme fibrosis is strikingly depicted by comparative photomicrographs of these three cases (Figs. 2, 3, and 4). At the same time it should be noted that, although the cellular reaction is much more prominent than the degree of fibrosis initially and while the fibrosis far exceeds the cellular element in the more chronic stage, in each instance features of both early and advanced disease were demonstrated. Such findings afford rather conclusive evidence that even in the very chronic case the original etiologic factor is by no means burnt out but is still in operation.

Just what this etiologic factor may be has not been clarified by an analysis of these cases. In none of these patients could a significant occupational or environmental exposure be elicited. The repeated culture of Staph. aureus from the sputum

in Case 1 might lead one to hypothesize that the disease represented a hypersensitivity to this organism. However, other than to mention the possibility of this occurrence, we see little point in elaborating on this concept. Except for the intermittent sweats and fever early in the course of Cases 1 and 3, there is little to substantiate an infectious origin, and these episodes like the terminal febrile response might well be explained by secondary infection. Histologically, except for the terminal phase in Case 3, neither an acute inflammatory nor a granulomatous reaction could be found and organisms were not demonstrated in tissue sections. Although Nocardia asteroides was cultured after death from the lungs of the second patient, the absence of mycelial filaments in specially stained lung tissue sections casts serious doubt as to the possibility of this organism being anything more than a tracheobronchial inhabitant. While a viral etiology has not been disproved, the long duration and gradual progression of the pulmonary process in the latter two patients, as well as the absence of viral inclusion bodies in every case, would appear to render this likelihood rather dubious. As to the possibility of this being a collagen disease of the lungs (Breckenridge [17]), we do not feel qualified to express a definite opinion. Case 1 did show a persistent hyperglobulinemia, and Case 3 an interstitial infiltration with eosinophiles demonstrated in the lung biopsy, but, in spite of a concerted search, no fibrinoid degeneration of the arterioles could be demonstrated. Actually, we are unable to find any clear evidence either favoring or refuting this view.

From a pathological study of these cases, the limitations of cortisone and corticotropin therapy are quite obvious, for these agents, though instrumental in retarding fibroblastic proliferation, are incapable of lysing fibrous tissue previously laid down. The incredible roentgenographic response to cortisone manifested by the first patient, in whom the pathology was primarily that of round cell infiltration and early fibroblastic proliferation, and the lack of an appreciable roentgenographic clearing in the more chronic cases aptly demonstrate that therapy, if it is to be effective, must be instituted early. This fact is of the utmost significance, for, as we have pointed out, the administration of cortisone and corticotropin to these patients is not without extreme danger and certainly should not be prescribed unless there is reasonable hope of improvement.

Despite the remarkable response to corticotropin in this one case, of far greater importance is the violent exacerbation and death which followed the withdrawal of, or reduction in, cortisone and corticotropin therapy. Admittedly, in Case 3, indictment of so slight a decrement in corticotropin dosage as the precipitating factor in the patient's death is open to question, but it cannot be disregarded. That the lungs can serve as the "shock organ" following hormone withdrawal has not heretofore been appreciated. A similar but milder reaction has been reported after decreasing corticotropin dosage in the treatment of berylliosis.[24] It has also been alluded to previously by Keeton's group,[25] who reported dramatic but nonfatal respiratory symptoms induced by the sudden termination of corticotropin therapy in the treatment of one case of diffuse indeterminate pulmonary fibrosis and in

24. Dobson, R. L.; Weaver, J. C., and Lewis, L.: Beryllium Granulomatosis Complicated by Tuberculosis: Report of a Case Treated with ACTH, Ann. Int. Med. **38**:312-325 (Feb.) 1953.

25. Keeton, R. W.; Best, W. R.; Hick, F. K.; Montgomery, M. M., and Samter, M.: Dramatic Respiratory Symptoms Induced by Sudden Withdrawal of ACTH, J. A. M. A. **146**: 615-616 (June 16) 1951.

another of chronic bronchitis and emphysema. The precise mechanism of this response remains as uncertain as the etiology of the underlying disease. Keeton's group [26] concluded that the rapid recovery upon resumption of corticotropin implied a pituitary rather than an adrenocortical deficiency. Although a suppression of corticotropin output accompanies cortisone administration, a pituitary deficit in our patients would seem unlikely, since prompt and vigorous corticotropin therapy failed to alter the terminal course. To indict an adrenocortical deficiency, such as supposedly accounts for the "postcortisone withdrawal syndrome" following treatment of rheumatoid arthritis, gout, etc., would likewise seem unwise in the presence of apparently normal adrenal glands. Finally, the possibility that these patients succumbed to an overwhelming infection that had been initially masked by cortisone and ACTH would seem to be ruled out rather effectively by negative bacteriological studies, including specially stained lung sections.

As best we can ascertain, it seems probable that in these three examples of the Hamman-Rich syndrome the basic underlying pathology, whatever its etiology, was variably suppressed during cortisone administration but became explosive in character when liberated from exogenous and possibly endogenous adrenocortical control. It is important to recall that these patients so often have a borderline respiratory reserve to begin with that a relatively slight degree of aggravation, whether by hypersensitivity or infection, may be enough to throw them into complete respiratory insufficiency.

CONCLUSIONS

At the present time we entertain considerable doubt as to the wisdom of utilizing hormone therapy in any but the most desperately ill patients with the Hamman-Rich syndrome, and we feel certain that, once instituted, a permanent maintenance dose of cortisone will be required. We even wonder whether endocrine therapy may not in some instances lend momentum to an already downhill course. The report of Keeton and co-workers [25] ended with the authors in a similar dilemma, for in one of their patients hormonal therapy could not be discontinued because of violent respiratory symptoms precipitated by each attempt to withdraw corticotropin. They stated that they hoped gradually to decrease and finally to terminate use of the drug altogether, but, insofar as we know, the success or failure of their attempt has never been reported. Certainly, in the light of these results hesitancy must be advised in utilizing these hormones and considerable discretion should be exercised in the selection of patients. Only time will tell whether the benefits of cortisone and corticotropin can be maintained in cases of this type without an ever increasing dosage requirement and a constant danger of exacerbating rather than controlling the disease.

Whatever the basis for these three deaths, certain implications are inescapable. Recourse to cortisone or corticotropin therapy in the treatment of diffuse pulmonary disease of undetermined etiology should not be undertaken lightly or injudiciously, especially when the clinical picture is compatible with the Hamman-Rich syndrome. Patients with asymptomatic and mildly symptomatic cases of diffuse indeterminate pulmonary disease should not be subjected to endocrine treatment, since the majority pursue a relatively benign course, as Chaves and Abeles [26] have recently

26. Chaves, A. D., and Abeles, H.: Disseminated Nodular Pulmonary Infiltrations of an Indeterminate Nature in Apparently Healthy Persons, Am. Rev. Tuberc. **65**:129-141 (Feb.) 1952.

demonstrated. Patients with long-standing disease should probably not receive cortisone or corticotropin, since well-established fibrosis precludes any significant improvement and the most one can hope to gain is an arrest or deceleration in the progression of the disease. If hormone therapy is decided upon, preferably in the early severe case, streptomycin should be administered concomitantly. On the basis of our experience, which is admittedly limited, we believe that no matter how slowly these agents are interrupted serious withdrawal symptoms can be anticipated in many patients with the Hamman-Rich syndrome and, for that reason, once endocrine therapy has been instituted it would seem advisable to continue its use indefinitely. In the event that withdrawal is attempted, the cessation of cortisone must be interminably protracted in an effort to accommodate the adrenal cortex to a gradual resumption of its normal function, an effect augmented by small doses of corticotropin. At the first evidence of an unfavorable trend, both cortisone and corticotropin should be reinstituted promptly and in very large doses with broad-spectrum antibiotic therapy.

SUMMARY

Diffuse interstitial pulmonary fibrosis of the type originally described by Hamman and Rich has been redefined in the light of subsequent reports and our own personal experience.

For the sake of both conciseness and clarity we propose as a more apt designation for this condition the term "Hamman-Rich syndrome."

On the basis of two deaths following cortisone withdrawal and a third following a slight decrease in corticotropin (ACTH) dosage, we question the advisability of so treating any but the most desperately ill patients with diffuse indeterminate pulmonary fibrosis. If these endocrinal agents are utilized, a permanent maintenance dose is advocated; should withdrawal be contemplated, the utmost caution is urged.

Dr. Charles A. Jones, Chief of Medicine, Veterans Administration Hospital, New Orleans, gave permission to use Cases 1 and *3*; Drs. Edward deS. Matthews and Oscar Blitz allowed us to include their case in this report (Case *2*), and Mr. Frederick W. Busic provided photographic assistance.

ADDENDUM

Since submitting this manuscript for publication we have learned that a brother of J. W. S. (Case 3) has recently been hospitalized in Chicago with a clinically indistinguishable pulmonary disease. Certainly this is a most fascinating development.

Moreover, our inference that the Hamman-Rich syndrome may not be as rare as it is thought to be gains further support from the appearance of four additional cases in the literature,[27] bringing to 25 the number of reported cases. One of these [27a] patients received cortisone for two months during the late stage of the disease. No significant benefit was obtained; fortunately therapy was discontinued without incident.

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27. (*a*) Silverman, J. J., and Talbot, T. J.: Diffuse Interstitial Pulmonary Fibrosis Camouflaged by Hypermetabolism and Cardiac Failure: Antemortem Diagnosis with Biopsy and Catheterization Studies, Ann. Int. Med. **38**:1326-1338 (June) 1953. (*b*) Golden, A., and Bronk, T. T.: Diffuse Interstitial Fibrosis of Lungs: A Form of Diffuse Interstitial Angiosis and Reticulosis of the Lungs, A. M. A. Arch. Int. Med. **92**:606-615 (Nov.) 1953.

MYOGLOBINURIA

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MYOGLOBINURIA is, as the name suggests, excretion of muscle coloring matter in the urine. It is not an illness *sui generis* but only a symptom of a disease process in the muscles, just as hematuria is indicative of a morbid change in the urogenital apparatus. One can distinguish four different types of myoglobinuria.[1]

1. Traumatic myoglobinuria, which may be caused by
   (*a*) Crush injury
   (*b*) High voltage accident
   (*c*) Arterial occlusion with ischemia
2. Myositis myoglobinurica
3. Haff disease
4. Paroxysmal myoglobinuria

Crush injury is a syndrome[2] which was already described in 1916, but during the last war more interest has been taken in it. In widely spread traumatic muscle injuries myoglobin may be found in the urine. Then a renal injury arises, with oliguria, isosthenuria, and azotemia. The mortality rate is high, and the patients often die on the 7th to the 10th day. By study of microscopic sections one finds the musculature discolored and necrotic in the injured regions and tubular nephritis in the kidneys. The renal injury is due to precipitation of myoglobin in the urinary canals and to acids produced by muscle metabolism.

In its commencement, course, and pathological anatomy myositis myoglobinurica is altogether like acute polymyositis. The only difference is that myoglobinuria is never observed in polymyositis. Up to now only two cases have been described in this group (Günther, 1923; Paul, 1924).[3]

Haff disease[4] was first observed in the years 1924-1925 at Frisches Haff, in East Prussia. The cause is probably connected with the eating of certain varieties of fish, especially the liver of burbot, but this has not yet been proved.

From Garnisonssjukhuset, Sollefteå (Dr. F. Möller, Director) and the Department of Medicine, Centrallasarettet, Västerås (Dr. A. Bjure, Director).

1. Biörck, G.: On Myoglobin and Its Occurrence in Man, Acta med. scandinav., Supp. *226*, p. 1, 1949.

2. Bywaters, E. G.; Delory, G.; Rimington, C., and Smiles, J.: Myohaemoglobin in the Urine of Air Raid Casualties with Crushing Injury, Biochem. J. **35**:1164-1168, 1941. Bywaters, E. G., and Beall, D.: Crush Injuries with Impairment of Renal Function, Brit. M. J. **1**:427-432, 1941.

3. Günther, H.: Kasuistische Mitteilung über Myositis myoglobinurica, Arch. path. Anat. **251**:141-149, 1924. Paul, F.; Über einen Fall von paralytischer Hämoglobinurie beim Menschen, Wien. Arch. inn. Med. **7**:531-554, 1924.

4. Berlin, R.: Haff Disease in Sweden, Acta med. scandinav. **129**:560-572, 1948.

The fourth and last type is paroxysmal myoglobinuria, which I shall describe in more detail, as my cases are of this type. Up till now only nine cases of this illness have been described.[5] The patients unaccountably begin to get an ache and a drawing feeling in the musculature, which generally begins in the calves. In the most serious attacks the patients have been completely paralyzed and have had to lie in bed for weeks or months before the trouble has fully gone. From a few hours up to 24 hours after the beginning of the attack a dark brown urine is produced, which gives a strongly positive benzidine test but has only a few isolated red blood corpuscles in the sediment. Generally tests for albumin are positive, at any rate in the beginning of the attack. The etiology is unknown. The prognosis has, with the exception of one case, been good *quoad vitam*, though the illness has a tendency to recur. In that one case the patient died with increasing uremia and the kidneys showed tubular nephritis.

REPORT OF CASES AND COMMENT

I myself have had the opportunity of seeing four verified cases of this illness. The first three cases are those of brothers.

CASE 1.—The patient was a 20-year-old youth. His parents are living and healthy, but the mother has diabetes which does not call for treatment with insulin. The patient is the fourth of the five brothers; he has one sister. Two of the brothers have the same trouble as the patient, but the rest are healthy. No nerve or muscle illnesses are known in the rest of the family or in the relations. Since the age of 15 the patient has often had an ache and a sense of fatigue in the musculature accompanying exertion, which were sometimes so severe that he could barely move. Only with the greatest difficulty could he get home when he had been out and played games, and sometimes he had to be helped the last part of the way. The ache always begins in the calves and the muscles of the thigh, which feel hard and sore, but it may afterwards move upwards and even affect the muscles of the upper extremities and sometimes even the intercostal muscles and the chewing muscles. Three to four hours after the symptoms have begun the patient produces a dark brown, often thick, urine and has at the same time a strongly increased thirst. The trouble then decreases, and after a few days to a week he is trouble-free again. The trouble only comes at times of muscular effort, and the patient, who is an active games man, attributes it to straining himself on an empty stomach. He has once or twice attended a physician for this and the diagnosis has each time been acute glomerulonephritis. On April 10, 1945, the patient was called up to serve in the Västernorrland regiment at Sollefteå. He got along very well in the first weeks, but on May 5, 1945, during a march, the trouble started again and gradually increased so that only with difficulty could the patient get home without help. After a few hours he passed dark brown urine. He was admitted to the regimental hospital. His urine was then red-brown, and Ehrlich and Schlesinger tests were positive. Tests for albumin were positive, but there was nothing abnormal in the sediment. The patient was sent to

5. Bywaters, E. G., and Dible, J. H.: Acute Paralytic Myohæmoglobinuria in Man, J. Path. & Bact. **55**:7-15, 1943. Debré, R.; Gernez, C., and Sée, G.: Crises myopathiques paroxystiques avec hémoglobinurie, Bull. Soc. méd. hôp. Paris **58**:1640-1649, 1934. Hittmair, A.: Haemoglobinuria paroxysmalis paralytica, Wien. klin. Wchnschr. **38**:431-434, 1925. Huber, J.; Florand, J.; Lièvre, A., and Néret, M.: Crises myopathiques paroxystiques avec hémoglobinurie, Bull. Soc. méd. hôp. Paris **62**:725-730, 1938. Kreutzer, F. L.; Strait, L., and Kerr, W. J.: Spontaneous Myohemoglobinuria in Man, Arch. Int. Med. **81**:249-259, 1948. Louw, A., and Nielsen, H. E.: Paroxysmal Paralytic Hemoglobinuria, Acta med. scandinav. **117**:424-436, 1944. de Langen, C. D.: Myoglobin and Myoglobinuria, ibid. **124**:213-226, 1946. Millikan, G. A.: Muscle Haemoglobin, Physiol. Rev. **19**:503-523, 1939. Scherwin, J.: Myoglobinuria paralytica, Nord. med. **24**:460, 1945. Meyer-Betz, F.: Beobachtungen an einen eigenartigen mit Muskellähmungen verbundenen Fall von Hämoglobinurie, Deutches Arch. klin. Med. **101**:85, 1916.

Garnisonssjukhuset on May 5, 1945, for investigation of an increased sedimentation rate (44 mm. in one hour). When he was taken into the hospital he was completely free from trouble and had no symptoms from the musculature. From the patient's history we suspected some form of paroxysmal hemoglobinuria or myoglobinuria. Cardiac, pulmonary, abdominal, and reflex studies revealed no abnormalities. The blood picture was completely normal. A Wassermann test was negative. The Donath-Landsteiner reaction was negative. The urine contained no bile pigment, and the Almén test for albumin was negative. The benzidine test for blood in the urine was negative. Direct-reacting bilirubin in the serum was 0.247 mg., and indirect-reacting bilirubin was 0.717 mg. per 100 cc. On May 16 hemolysis began at 0.60% and was complete at 0.44% NaCl. On May 17 hemolysis began at 0.55% and was complete at 0.40%. The sedimentation rate at the time of admission was 30 mm., but after a few days it was 8 mm. in one hour. The only abnormality one could find at this time was a slight reduction of the resistance of the blood cells and a slight increase of the sedimentation rate. On May 23, 1945, the patient had a hard duty with cross-country running and football, and at about 4 p. m. he began to get an ache and a sense of fatigue in the calves, which spread up to the musculature of the thigh and the back. The ache, the stiffness, and the sense of fatigue spread later on so that only with the greatest difficulty could he get home and up the stairs. At about 6 p. m. on the same day he passed dark brown urine. On May 24 he was again admitted to Garnisonssjukhuset. He felt well and could walk without any trouble. There was some tenderness in the musculature of the arms and the legs, but other than this nothing special could be found at an ordinary examination. There was no paralysis, and the reflexes were normal. Immediately after admission the patient passed dark brown urine. The urine contained albumin (1+) and the benzidine test was positive (2+); a few red blood cells and granular casts were found in the sediment. The Ehrlich test was positive and the Schlesinger test showed a slight trace of urobilin, but otherwise results of studies of gallbladder function were normal. The day after admission the urine was a normal color again and the benzidine test was negative. On May 25 direct-reacting bilirubin in serum was 0.681 mg. and indirect-reacting bilirubin was 1.050 mg. per 100 cc. On May 29 these values were 0.750 mg. and 1.323 mg., respectively. Prothrombin time (Quick) was 94%, phosphatase (Buch) 6 units, amylase (Nøreby) 0.0035, and hippuric acid synthesis normal. The Takata test was negative. The patient was discharged without any symptoms on June 1, 1945. On Sept. 10 he had a similar attack and was then examined in the outpatient department of the hospital. On admission he was completely without symptoms, but the urine was the color of porter and contained albumin (Heller test, 1+) and blood (benzidine test, 2+). The sediment contained a few red corpuscles. Hemolysis of the blood corpuscles began at 0.40% and was complete at 0.30% NaCl. Direct-reacting serum bilirubin was 0.382 mg., and indirect-reacting bilirubin was 0.678 mg. per 100 cc. The white blood cell count was 12,300. The differential cell count showed 75% segmented neutrophiles, 5% band neutrophiles, 6% monocytes, 14% lymphocytes, and 0% eosinophiles. The blood pressure was 145/100. Nonprotein nitrogen of undetermined origin (resting N) was 35 mg. per 100 cc. An electrocardiogram was interpreted as showing no abnormalities. At a control examination one week later the blood pressure was 115/75 and the white cell count was 5,800. On Nov. 22 a urine specimen taken during the attack-free interval (in which the Heller and benzidine test were negative, the Ehrlich test 1+, and the Schlesinger test 2+) was sent to Prof. Hugo Theorell for analysis for myoglobin, which was negative. After the last attack the patient was placed on fatigue duty, which he did without any trouble. On Dec. 10, 1945, he joined in a ski run of 6 km., which was followed by a complete attack. In a urine sample sent to Professor Theorell for analysis, myoglobin could be seen spectroscopically for certain. Creatinine concentration in urine during the attack was 47 mg. per 100 cc.; during the free interval the concentration was 1 mg.

Microscopic examination (by Professor Gellerstedt) of a biopsy specimen taken from the calf muscle during a free interval gave these results: The musculature is in very good condition generally and excellently attached. No difference in coloring between the preparations appears for certain. The only thing which may be characterized as pathological on comparison with other skeleton muscle preparations is that nuclei of the sarcolemma seem generally increased (in cross section pictures) and also apparently are unevenly distributed (by longitudinal section). The fine connective tissue between the isolated muscle threads is possibly a little increased. Aside from that, the striated structure and muscle fibers appear to be normal.

Urea clearance was normal. A basal metabolism test was +8%. An x-ray was negative for calcifications in the musculature. No porphyrin was found in the urine either during or between the attacks. Glucose determination during the free interval showed that the fasting blood sugar level was pathologically increased (167 mg. per 100 cc.) but became lower when the patient was given glucose (Fig. 1).

Case 2.—The patient was a 19-year-old youth. His trouble began at the age of 16 to 17 years and has been of exactly the same character as that of his other brothers. This patient is also an active sportsman. He has never had any severe attacks. After a few days he always used to be well again. He has said that he always gets the trouble if he strains himself on an empty stomach. Sometimes he has even had trouble in swallowing during the attacks. In 1942 the patient was in the hospital for this trouble and it was diagnosed as acute nephritis. In February 1946, during a free interval, a urine specimen was examined; the Schlesinger test was 2+ but there were no other abnormalities. The examination for myoglobin during the free interval was negative (Professor Theorell). On April 28, 1946, an examination for glucose was made in the outpatient department and the results showed the same pattern as for the first brother, in this case a fasting blood sugar level of 147 mg. per 100 cc., which went down when the patient was given glucose (Fig. 2). On May 21, 1946, he was admitted to Garnisonssjukhuset, Sollefteå, for further examination. He was completely free from trouble when he was taken

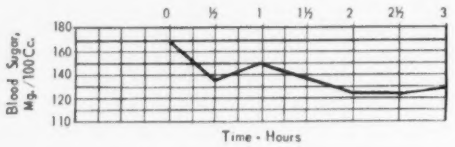

Fig. 1 (Case 1).—Glucose-tolerance curve.

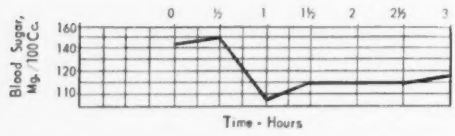

Fig. 2 (Case 2).—Glucose-tolerance curve.

into the hospital. Cardiac, pulmonary, abdominal, throat, and reflex studies revealed no abnormalities. The blood pressure was 120/75. Urine studies on admission showed the Schlesinger test to be 3+; the Harrison, Hay, Hammarsten, Jod, and Ehrlich tests were negative. The Almén hospital stay the urine urobilin was 2 to 3+. At the time of admission the hemoglobin was 94%, red blood cell count 5,120,000, white blood cells 6,300, and reticulocytes 2%. The differential cell count was normal. Bile pigment in the serum (Meulengracht's method) was 4 units; the sedimentation rate was 1 mm. Hemolysis of red blood cells began at 0.48% and was complete at 0.35% NaCl. On June 3 the urea clearance was normal. The basal metabolic rate was —3%. On the basis of the patient's history, that he always became ill when straining himself on an empty stomach, and also on the basis of the paradoxical glucose-tolerance curves, it seemed probable that the illness was connected with abnormal carbohydrate metabolism. For that reason the patient was given food with no carbohydrates from the morning of June 3 and was confined to bed to eliminate all body exertion. He felt very well all that day and even on the morning of June 4, when liver tests were made. The results showed 0.556 mg. direct-reacting and 1.543 mg. indirect-reacting bilirubin per 100 cc. The icterus index was 17 (on admission it was 4). Phosphatase was 5.6 units (Buch), prothrombin time 100% (Quick), amylase 0.0042 (Nøreby), and hippuric acid (Takata) normal. In the evening of June 4 the patient felt a little tired and unwell. He went to sleep but woke up at 2 a. m. with a severe ache in arches and legs and gradually increasing difficulty in breathing. Nostril breathing was dif-

ficult, and he had to use the scalenus muscles. He had no cyanosis, and it seemed that because of the pain he tried to keep his chest still while breathing. He said that he not only had pain but that he could not manage to draw his breath completely. At this time he had a temperature of 39 C. and his pulse rate was 120. An electrocardiogram showed tachycardia but no other abnormality. Because of the threatened paralysis of the breathing musculature and because it was impossible to know how far the paralysis would advance, the patient was moved to the isolation hospital, in case he needed a respirator. At 8 a. m. June 5 the patient was still in bed, with irregular breathing but no cyanosis. The temperature was then 37.5 C., and pulse rate 120. The patient was apathetic and could only say a few words at a time, but he complained about severe aches all over his body. He had difficulty in chewing and could only have liquid food. He could not move his legs at all but could lift his arms 2 dm. from the bed. Patellar and tendon reflexes in the arms were weak but bilateral. The Achilles and abdominal reflexes were normal. Superficial and deep sensibility was normal. At 10 a. m. on June 5 the patient produced 260 cc. of porter-colored urine, in which benzidine was 3+ and there were red blood cells and granulous and hyaline casts in the sediment. Blood tests at that time showed hemoglobin 96%, red blood cells 5,450,000, and white blood cells 16,700, with a differential cell count of 78% segmented neutrophiles, 10% band neutrophiles, 3% monocytes, and 9% lymphocytes. Rest N was 35 mg. per 100 cc. The patient was given a large amount of dextrose by mouth and intravenously and even bicarbonate to make the urine alkaline and to prevent precipitation of myoglobin into the urinary canals. After bicarbonate was administered, the urine was clear and had not the thick sediment of crystals that it had before but it was still cherry-red. During the night of June 6 the patient slept poorly and had two sudden attacks in which he became cold and had a slow pulse rate (44 per minute). He improved quickly, and the pulse rate rose again, to 120. Apart from tachycardia repeated examinations with the electrograph showed nothing abnormal. Urine specimens, examined by Professor Theorell,[6] proved to be completely free from hemoglobin, and it was possible to prepare crystalline myoglobin from the urine. Determinations of urine porphyria and creatinine during the attack showed a small trace of uroporphyrin but no coproporphyrin. Creatinine was 146 mg. and creatine 137 mg. per 100 cc. During a free interval no uroporphyrin or coproporphyrin was demonstrated, creatinine was 190 mg., and creatine was 2 mg. per 100 cc. On June 7 the white blood cell count was 16,500, with differential cell count of 70% segmented neutrophiles, 10% band neutrophiles, 9% lymphocytes, and 1% monocytes. The icterus index (Meulengracht) was 7.5. The blood pressure was 150/100; on admission it was 120/75. On June 8 the patient was still very tired, but he could freely move his extremities, although his strength was extremely poor. Beginning June 8 he was given an injection of 3 cc. of a preparation containing 60% adenosine triphosphate (Adynol [Astra]) daily, and the next day the muscle pains were gone and the urine was a normal color again. He gradually improved, and on June 14 he could walk freely. He was discharged on June 15, but he still felt tired. Blood studies on June 15 showed no abnormalities. The sedimentation rate was 27 mm.

Case 3.—The patient was born in 1919. He was in Garnisonssjukhuset at Sollefteå May 6 to 16, 1941. He was admitted by a military doctor because his urine after exertion was "bloody." He said then that several times after long ski runs he felt very tired and had a pain in his back and bloody urine. On admission there were no complaints aside from the pain in his back. There was albumin in the urine; the sediment contained a few red blood cells and granular casts. Rest N was 32 mg. per 100 cc. Results of a concentration-dilution test showed dilution to 1.011 and concentration to 1.021. The patient was discharged with the diagnosis nephritis chronica exacerbans and was declared unfit for military service. Since then he has had similar attacks, with dark urine and pain in his back and sometimes also in other muscles. The trouble has been of the same type as his brothers', but he has only had slight attacks. He has also noticed that he more readily has trouble after effort on an empty stomach. He was twice in the hospital for this trouble, with the diagnosis of nephritis. Urine examined during a free interval showed urobilin 2+ and no other abnormalities. He was not examined more thoroughly.

6. Theorell, H., and de Duve, C.: Crystalline Human Myoglobin from Heart Muscle and Urine, Arch. Biochem. **12**:113-124, 1947.

To summarize these three cases, it may be pointed out that the disease presented is a familial form of paroxysmal myoglobinuria beginning about puberty. The pathogenesis is probably a disturbance in carbohydrate metabolism, as the three following facts indicate: (1) the information in the patients' histories that they always used to get the trouble when they played games on an empty stomach, (2) the paradoxical glucose-tolerance curves, and (3) the provocation of attacks with carbohydrate-free food.

The increased proportion of urobilin in the urine is noticeable even between attacks. Urobilin may be interpreted as a breakdown product of myoglobin and accordingly indicates that myoglobin lysis is going on also between the acute attacks, although not in so great a degree that myoglobin appears in the urine.

It is possible and perhaps also more probable that urobilinuria is caused by the disturbed carbohydrate metabolism. That urobilinuria appears when there is a reduction of carbohydrates in the food is a well-known fact.[7] The paradoxical glucose-tolerance curves show, for the rest, that a pathological conversion of carbohydrate takes place during the trouble-free interval. On several occasions I have also noticed that urobilinuria, which during the free interval may have been important, decreased considerably during the major attack. This perhaps may be interpreted as a sign of kidney injury, with a consequent excretion of urobilin. As already is known, the Schlesinger test may be negative in acute hepatitis complicated with nephritis. The increased sedimentation rate associated with the attacks occurs when free myoglobin is present in the circulating blood. This probably is analogous to the situation in which there is free hemoglobin in the blood, which, as Fahraeus has shown, brings out an increased quantity of fibrinogen and in that way increases the sedimentation rate.

I shall now describe the fourth case of myoglobinuria from Centrallasarettet, Västerås, during the period from Dec. 29, 1949, to Jan. 13, 1950.

The patient is a 35-year-old mosaic worker. There is no known hereditary disease in the family history. The patient was healthy as a child and during military service was quite capable of bearing arms. In 1938 he was treated in the surgical clinic, Centrallasarettet, Västerås, for muscle rupture in the right lower leg, and in 1940 for muscle rupture in the left lower leg. Otherwise he has been fairly healthy, but since 1945 he has on four different occasions been ill with sudden severe muscle pains, a high temperature for a few days, and brown urine. He was treated in another hospital for this trouble from Dec. 24, 1945, to Feb. 1, 1946, with the diagnosis of acute glomerulonephritis and bilateral sciatica. A few days before admission he had aches in his arms and legs and a temperature of about 40 C. He felt unwell and had attacks of vomiting, and he also had brown urine. On admission the urine was free from albumin; the sediment contained some red blood cells but was not otherwise abnormal. On Jan. 2 there was a trace of albumin and four or five red blood cells in the sediment but no other abnormality. On Jan. 3, 1946, the rest N was 180 mg. per 100 cc. Rest N was increased for a time, and on Jan. 10 it was 138 mg., on Jan. 16 it was 80 mg., on Jan. 23 it was 40 mg., and on Feb. 1 it was 30 mg. All during this time tests for albumin were negative, except on Jan. 2, when there was a trace of it. The highest sedimentation rate was 55 mm. The blood pressure remained normal (120/70) during this time. Unfortunately, the specific gravity was not determined. The patient was also treated for this trouble at the medical clinic, Centrallasarettet, Västerås, from May 5 to 7, 1947, with the diagnosis of lumbago, sciatica, and bronchopneumonia. On admission he was trouble free, but some time before that he had had trouble with aches in his back, thighs, and upper

7. Bang, O.: Klinische Urobilinstudien in Sonderheit an normalen und "lebergesunden" Personen: Die Wirkung kohlehydratknapper Kost auf die Urobilinausscheidung; Die Urobilinurie der Diabetiker, Acta med. scandinav., Supp. 29, pp. 9-203, 1929.

arms. A test for albumin was negative. Rest N was 28 mg. The specific gravity of the urine was 1.028. The patient was treated again at the medical clinic from June 20 to 30, 1947, without any objective symptoms being found.

On Dec. 24, 1949, the patient began to have stiffness in his musculature, which increased so that finally his muscles were as hard as stone and swollen. He had a temperature of 39.2 C., which after a day went down to 38 C. On Dec. 25 the patient noticed that his urine was as dark as light beer. The urine began to become lighter and the pains in the musculature decreased so that on admission, Dec. 29, 1949, the patient was trouble free and the urine was very nearly a normal color.

At the time of admission the test for albumin was positive, the sediment showed nothing pathological, and rest N was 43 mg. per 100 cc. The concentration-dilution test showed almost a condition of isosthenuria (dilution to 1.009 and concentration to 1.016). Creatinine clearance was 132 ml. per minute. The test for albumin was negative after two days. On Jan. 1, 1950, rest N was 44 mg., and on Jan. 10 it was 34 mg. per 100 cc. Another concentration-dilution test, on Jan. 11, gave the same result as before (dilution to 1.009 and concentration to 1.013). The blood pressure was normal (120/80). The icterus index (Meulengracht) was 4 on Dec. 30, 1950. The sedimentation rate on admission was 32 mm. and on discharge was 62 mm. The glucose-tolerance curve was normal. On admission the benzidine test for blood in the urine was positive and spectroscopic examination (Prof. G. Blix, Uppsala) showed a large amount of myoglobin. The test for uroporphyrin was negative. The patient was discharged as trouble free.

This case is different in several ways from the other three cases. This patient has not noticed that muscle effort or effort on an empty stomach have any significance for the genesis of the attacks, which was a characteristic of the other cases. This patient had normal glucose tolerance. No increase in bilirubin in the serum or increased excretion of urobilin in the urine has been proved. In this case the determination of urobilin was made because the patient had a verified kidney injury eight days after the attack, which might possibly have upset the result. No attempt to bring on an attack with carbohydrate-free food was made. The kidney injury in this case was quite typical for distal tubular nephritis.[8] The pathogenesis is probably not the same as in the other three cases, but the dominating symptoms, with muscle pains and dark brown urine, make the syndrome so similar in character that one has reason to expect a similar genesis.

As to differential diagnosis, there are only three diseases, namely, porphyrinuria, acute glomerulonephritis, and different forms of hemoglobinuria, which are worthy of discussion. It is natural to suspect porphyria in the case of a fully developed attack, with muscle ache, paralysis, and dark urine. The diagnosis can be confirmed by a chemical analysis of urine, for a positive benzidine reaction without red blood corpuscles in the sediment will only occur in myoglobinuria or hemoglobinuria and never in porphyrinuria. In case of clear muscular symptoms the presence of hemoglobinuria is improbable and the establishment of the presence of myoglobin by spectroscopic analysis will verify the diagnosis. In a mild attack, with only a mild discoloring of the urine or when the patient still has normal colored urine, one will suspect acute nephritis. A positive Heller test, a few red corpuscles and granular casts in the sediment, and perhaps increased rest N will further corroborate the diagnosis of acute nephritis. When at the beginning of attacks there is occasionally

8. Burch, G. E., and Ray, C. T.: Lower Nephron Syndrome, Ann. Int. Med. **31**:750-772, 1949. Lucké, B.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), Mil. Surgeon **99**:371-396, 1946.

a slight increase in blood pressure, the diagnosis becomes even more difficult. The kidney lesion in myoglobinuria is always of the type of distal tubular nephritis and not acute glomerulonephritis.

SUMMARY AND CONCLUSIONS

Four cases of myoglobinuria are described. In the first three patients, who are brothers, the cause probably is a disturbance in carbohydrate metabolism, as indicated by the paradoxical glucose-tolerance curves and the provocation of attacks with carbohydrate-free food. All four patients have been treated repeatedly in different hospitals under the diagnosis of acute glomerulonephritis. It is certain that the paradoxical condition of myoglobinuria is commoner than the occurrence of only nine previously published cases indicates. There are presumably a number of patients with myoglobinuria treated in hospitals for glomerulonephritis.

ANTIBIOTIC PROPHYLAXIS IN CHRONIC RESPIRATORY DISEASES

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THE PROBLEMS of present-day medicine are rapidly becoming those of an aging population. Virtual eradication of many common infectious diseases together with the development of improved standards of nutrition, general hygiene, employment, and housing have resulted in progressive lengthening of human life. Today it is estimated that more than 7,000,000 persons in the United States are over 65 years of age; probably 1,000,000 have passed the 80-year mark.[1] This represents an increase of 30% in the past 10 years. A natural consequence of this development has been an increasing emphasis on those conditions which primarily afflict elderly persons.

One of the principal problems in geriatric medicine concerns the management of chronic respiratory diseases, such as chronic bronchitis, bronchial asthma, pulmonary emphysema, and bronchiectasis. It should be emphasized that these conditions also occur in the younger age groups. Until recently pulmonary emphysema was accepted as an utterly hopeless condition usually occurring in older persons. Therapy was essentially nil. However, in the past few years the pathologic physiology of this disabling condition has been exhaustively investigated.[2] As a result, treatment consisting of general hygienic measures, diet, and postural drainage has been supplemented by the development of specific and affective exercises which serve to increase the bellows motion of the diaphragm and chest wall.[3] In many cases, this has resulted in impressive clinical improvement. Various types of abdominal binders as well as pneumoperitoneum have proved to be of considerable value.[4] Although oxygen therapy may

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be life-saving, its potential danger in chronic emphysema has been clarified.[5] The demonstration that oxygen can cause carbon dioxide narcosis with mental aberration, coma, and even death in the face of severe respiratory distress is a most important contribution to modern therapy.

Frequently emphysema occurs in association with chronic bronchitis and bronchial asthma.[6] The latter conditions may have preceded the former by many years. Bronchiectasis is also present in a large number of such persons.[6] It is well to recall that bronchiectasis is said to be more common in certain parts of this country than pulmonary tuberculosis.[7] Until recently, this disease was considered to occur almost entirely in children and young adults; however, it is now being reported in ever increasing numbers of elderly persons.[8] Bronchiectasis may develop in middle and later life as a sequel or complication of recurrent respiratory infections, chronic bronchitis, repeated episodes of bronchial asthma, foreign body pulmonary fibrosis, or pulmonary emphysema.

The clinical picture in extensive chronic respiratory disease is as distressing as it is characteristic. The usual manifestations include constant cough which tends to become especially disturbing with changes of position, dyspnea, weakness, anorexia, malnutrition, anemia, weight loss, malaise, and mental apathy. Nausea and vomiting often accompany bouts of coughing. Semi-invalidism develops as extreme dyspnea accompanies even mild exertion; merely walking about the house becomes a definite chore, which severely taxes the patient's strength. In time pulmonary heart disease, cor pulmonale, may develop, with right ventricular failure. Of interest is the observation that cor pulmonale constitutes approximately 6% of all heart disease demonstrated at necropsy.[7] This type of congestive heart failure responds very poorly to digitalis and routine cardiac therapy. Relief depends upon improvement of the underlying pulmonary condition.[9]

One of the most distressing aspects of chronic respiratory disease is its psychological effect on the patient. Not only is the patient confronted by a serious economic problem resulting from his inability to work and his frequent hospitalizations, but, also, his intimate social contacts are threatened. Constant coughing with the production, in many instances, of large quantities of foul material tends to ostracize a person from society. The person with extensive pulmonary disease is not welcomed by his fellows and soon finds himself condemned to a lonely and solitary existence.

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9. Stone, P. J.; Schwartz, A.; Newman, W.; Feltman, J. A., and Lovelock, F. J.: Precipitation by Pulmonary Infection of Acute Anoxia, Cardiac Failure and Respiratory Acidosis in Chronic Pulmonary Disease: Pathogenesis and Treatment, Am. J. Med. **14**:14, 1953.

Despite recent medical progress, no cure exists for advanced pulmonary emphysema. Early bronchiectasis can be corrected by complete surgical eradication. Unfortunately less than 50% of cases appear to be suitable for surgery.[8] In many instances the disease process is too extensive for total eradication; in others, the physical condition of the patient may contraindicate surgical procedures or, frequently, submission to operation may be refused by the patient.

Of primary importance in the management of chronic pulmonary disease is the control of superimposed respiratory infections. These patients are quite susceptible to intercurrent or secondary pulmonic infections. Repeated bouts of acute bronchitis and bronchopneumonia are characteristic. Unfortunately, these persons have a very narrow margin of respiratory safety. Even very minimal bacterial involvement may result in severe dyspnea, which may necessitate complete restriction of activity; actual suffocation and death may rapidly develop. Recently it was emphasized that acute anoxemia, respiratory acidosis, and right heart failure can develop in an extremely brief period as the result of minimal secondary infection in patients with emphysema.[9] These patients may have previously disclosed little clinical evidence of dyspnea or right heart strain. It is extremely important to recall that aside from heart failure the chief cause of death in cor pulmonale is secondary respiratory infection.[7]

In the past, efforts have been made to control pulmonary infections in persons having underlying respiratory conditions by prompt and adequate treatment. Sulfadiazine, penicillin, streptomycin, and the broad-spectrum antibiotics have been employed with excellent results.[6] Unfortunately, improvement is only temporary. An additional and very important problem is the difficulty of diagnosing respiratory infections in geriatric patients having chronic pulmonary disease. Frequently there is little increase in cough and little or no chest pain, fever, or leucocytosis. In a recent report it was emphasized that acute respiratory insufficiency resulting from secondary infection in those who suffer from an underlying pulmonary disease may be confused with congenital heart conditions, acute pulmonary infarction, and even pericardial effusion with tamponade.[9]

It occurred to us that the most promising possibility for controlling dangerous intercurrent infections might be the long-term administration of a broad-spectrum antibiotic. In this manner, bacterial infections caused by Gram-positive and Gram-negative organisms might be reduced or even prevented. We had successfully treated 74 cases of acute bacterial pneumonia with chlortetracycline (aureomycin) and had observed its effectiveness against such common respiratory pathogens as the Pneumococcus, Micrococcus pyogenes var. aureus, Streptococcus pyogenes, and Klebsiella pneumoniae.[10] The value of this antibiotic in respiratory infections is well established.[11] In addition, we had been impressed by the absence of serious toxic reactions even when chlortetracycline was administered in large quantities and for prolonged

10. McVay, L. V., Jr., and Stern, T. N.: An Effective and Economical Method for Treatment of Acute Nontuberculosis Bacterial Pneumonia, Antibiotics & Chemother. **2**:215, 1952.

11. Gocke, T. M.; Collins, H. S., and Finland, M.: Aureomycin Treatment of Pneumococcic Pneumonia, Arch. Int. Med. **84**:857, 1949. Collins, H. S.; Gocke, T. M., and Finland, M.: Aureomycin Therapy of Nonpneumococcic and Nontuberculosis Bacterial Pulmonary Infections, ibid. **84**:875, 1949. Dowling, H. F.; Lepper, M. H.; Hussey, H. H.; Caldwell, E. R., and Spies, H. W.: The Treatment of Pneumococcic Pneumonia with Aureomycin, J. Lab. & Clin. Med. **35**:215, 1950.

periods.[12] No anaphylactoid reactions have been observed. When dosage in the range of 1 gm. daily was used, even minimal gastrointestinal disturbances were infrequent.[10] The danger of pulmonary moniliasis resulting from the use of a broad-spectrum antibiotic in a debilitating condition such as bronchiectasis or emphysema was thought to have been largely eliminated by the addition of the methyl and propyl esters of *p*-hydroxybenzoic acid (Paraben) to chlortetracycline.[13]

The present paper constitutes a report of the prolonged administration of chlortetracycline as a prophylactic agent to 30 persons having chronic respiratory disease. Inasmuch as the possible overgrowth of resistant organisms such as hemolytic strains of M. pyogenes var. aureus, Pseudomonas aeruginosa, and Proteus vulgaris leading to serious or fatal infection was regarded as the principal hazard involved in this investigation, comprehensive bacteriologic and sensitivity determinations are presented. Results of toxicity studies are also included.

METHODS

In order to determine the dosage of chlortetracycline [14] best suited for this study, various quantities were administered to hospitalized patients and serial blood levels were subsequently obtained. Using 50 mg. hourly for five hours, a concentration of 1 γ per cubic centimeter was obtained, which persisted for three to eight hours after the final dose; when 100 mg. was administered in the same manner, it was possible to maintain a concentration of 2 γ per cubic centimeter for one to four hours after the completion of medication. As a result of these observations, 250 mg. of chlortetracycline was administered before breakfast and again two hours after the evening meal to four patients; blood levels over a period of 24 hours ranged from 0.12 to 2 γ per cubic centimeter; no trace of the antibiotic could be demonstrated in one instance. This regimen was next employed in 12 ambulatory patients, and levels were found to vary from 0.06 to 4.0 γ per cubic centimeter over a period of 16 hours; no aureomycin was present in two instances. A review of the literature and our own in vitro studies suggested that these concentrations should suffice to forestall the majority of common respiratory infections.[15] Previous clinical observations indicated that this dosage of chlortetracycline produces minimal untoward effects.[10] Therefore, this regimen (250 mg. twice a day) was adopted for the present investigation. Only chlortetracycline containing Paraben was employed.[13]

In an attempt to eliminate unintentional bias and to obtain as objective results as possible, placebo capsules [16] were secured which were identical in appearance to the chlortetracycline preparation. Thereby, a control group of subjects could be observed for comparative purposes. Neither the patient nor the physician knew which preparation a given person was receiving.

12. McVay, L. V., Jr., and Carroll, D. S.: Aureomycin in the Treatment of Systemic North American Blastomycosis, Am. J. Med. **12**:289, 1952. McVay, L. V., Jr., and Sprunt, D. H.: Bacteroides Infections, Ann. Int. Med. **36**:56, 1952; A Long Term Evaluation of Aureomycin in the Treatment of Amebiasis, South. Med. J. **45**:183, 1952. McVay, L. V., Jr.; Guthrie, F., and Sprunt, D. H.: Aureomycin in the Treatment of Actinomycosis, New England J. Med. **245**:91, 1951.

13. McVay, L. V., Jr., and Sprunt, D. H.: A Study of Moniliasis in Aureomycin Therapy, Proc. Soc. Exper. Biol. & Med. **78**:759, 1951.

14. All preparations employed in this study were obtained through the courtesy of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

15. McVay and Stern.[10] Price, C. W.; Randall, W. A., and Welch, H.: Bacteriological Studies of Aureomycin, Ann. New York Acad. Sc. **51**:211, 1948. Bliss, E. A., and Todd, H. P.: A Comparison of 8 Antibiotic Agents, in Vivo and in Vitro, J. Bact. **58**:61, 1949.

16. The formula of the placebo capsules, expressed in milligrams per capsule, was anhydrous dicalcium phosphate, 689; magnesium stearate, 10; liquid petrolatum, 13; F. D. and C. yellow No. 5 dye, 1. Subsequently the formula was altered to anhydrous dicalcium phosphate, 360; magnesium stearate, 10 and liquid petrolatum, 10.

Thirty persons were obtained for study from the general medicine clinic, the thoracic surgery clinic, and the otolaryngology clinic of the John Gaston Hospital and the University of Tennessee College of Medicine. Only persons with far advanced and incurable conditions were included in this investigation. Twenty-nine persons had chronic bronchitis associated with extensive bilateral bronchiectasis, advanced emphysema, or recurrent and severe bronchial asthma. The diagnosis of bronchiectasis had been established in all instances by the use of bronchograms. The 13th patient (Case 3) had chronic otitis media and had suffered yearly episodes of acute purulent meningitis (pneumococcal meningitis twice and influenzal meningitis once) during the three preceding winter seasons. Because of the patient's condition and as a result of requests by physicians, 21 patients were included in the chlortetracycline-treated group and only 9 in the placebo-treated, or control, series. The average age in the chlortetracycline-treated category was 52.4 years, while that in the control group was 51.5 years. Four persons among those who received chlortetracycline were below the age of 45 years (13, 13, 22, and 39 years, respectively) as compared with two among the untreated patients, who were 31 and 42 years of age. The 21 persons comprising the chlortetracycline-treated series had been hospitalized on 32 occasions during the preceding three years because of respiratory infections; this averaged 1.5 hospitalizations per person. The total period of institutional care required during this interval had amounted to 413 days, or 19.7 days per patient. The nine persons in the placebo group had experienced 15 hospitalizations during the preceding three years, or 1.7 hospitalizations per person. Total days of hospitalization amounted to 131, or 15 days per person. Cor pulmonale was present in seven patients included in the chlortetracycline-treated group and in three of the controls. Digitalis, ammonium chloride, and low-sodium diet maintained a state of compensation in all but two subjects, who required frequent mercurial diuretics. Both of the latter persons were in the antibiotic-treated group. Eleven patients in the chlortetracycline-treated series were males, and 10 were females. Five of the controls were males, and four were females. Twelve of the patients who received chlortetracycline were white, while nine were Negroes, as compared with six white persons and three Negroes in the placebo category.

Each patient included in this study was examined at monthly intervals in the antibiotic clinic of the John Gaston Hospital and the University of Tennessee College of Medicine. At the time of each examination the following laboratory procedures were performed: determination of hematocrit level and sedimentation rate, white blood cell count, and urinalysis. Likewise, at intervals of three months the following determinations were performed: nonprotein nitrogen, serum bilirubin, sulfobromophthalein retention, cephalin flocculation, total and fractional plasma protein, cholesterol, and cholesterol esters. The sputum was collected regularly and was observed grossly for quantity, color, consistency, odor, and blood; the presence of polymorphonuclear leucocytes was determined microscopically. A vital capacity determination and an electrocardiogram were secured every three months. Roentgenograms were obtained as indicated.

RESULTS

The period of observation in this study ranged from two weeks to 20 months. The average in the chlortetracycline-treated group was 11 months, as compared with 7.7 months in the control series. Ten of the 21 patients who received chlortetracycline were followed for more than one year, as compared with only 3 in the placebo group.

Two deaths occurred during this investigation, one in each group. A brief summary of the single fatality in the chlortetracycline-treated group is presented.

This patient was a 43-year-old white man who had been a semi-invalid for approximately nine years because of extensive bilateral bronchiectasis and diffuse hypertrophic emphysema with associated chronic bronchitis. During the 12 months immediately preceding his inclusion in the antibiotic prophylactic study, hospitalization had been necessary on three occasions, for a total of 23 days. In addition, right-sided heart failure had required digitalization and frequent mercurial diuretics. From Nov. 27, 1951, through March 13, 1953 (15.5 months), this patient received 500 mg. of chlortetracycline daily. His previous therapeutic regimen was also continued. This consisted of frequent postural drainage, use of a supporting abdominal belt, regular respiratory exercises, expectorants, bronchodilators, and supplementary vitamins with an adequate

diet. After he began chlortetracycline prophylactic therapy, hospitalization was required only once. The cough became less marked, dyspnea became less severe, and the sputum was reduced by approximately 50%. Except for a brief interval of four days, polymorphonuclear leucocytes were essentially absent from the sputum. Of especial importance to the patient and his family was the fact that he was able to resume his occupation as a taxi driver; employment was continued until three weeks prior to death. Intractable cardiac decompensation was responsible for death. Necropsy in this case disclosed pronounced marginal bullous emphysema, with many large vesicles measuring up to 6 cm. in maximum diameter. Bronchiectatic involvement was demonstrated in all lobes but especially striking in the upper lobe of the right lung. Diffuse pulmonary fibrosis was present. There was no evidence of an acute inflammatory process; no bronchopneumonia was demonstrated. The right ventricle was greatly thickened and measured 0.8 cm. at the pulmonary conus. The remainder of the findings involving the liver, spleen, and extremities were those of right-sided failure.

The second death in this study occurred in the control group and is also briefly presented.

This patient was a 62-year-old white woman who had suffered two episodes of bronchopneumonia during the 24 months prior to admission to the antibiotic prophylactic program. The diagnosis of chronic bronchitis, bilateral emphysema, and extensive bronchiectasis had been established at the John Gaston Hospital in 1949. In January 1953 (after 13 months in the placebo series) bronchopneumonia developed in this patient while she was visiting in a neighboring city, and she died of respiratory insufficiency. Necropsy was not performed.

A definite reduction in the frequency and severity of respiratory infections was observed in 17 of those persons to whom chlortetracycline was administered; no change was noted in 4 (Table 1). No increase in incidence occurred in any patient

TABLE 1.—*Incidence of Respiratory Infections*

Series	Incidence of Respiratory Infections		
	Fewer	No Change	More
Chlortetracycline	17	4	0
Control	2	4	3

in the antibiotic-treated group. In the control group two persons had fewer respiratory infections and no change occurred in four, while there was a definite increase in three. It became necessary to transfer one patient from the control group to the antibiotic-treated group. This case is presented as an example of the effect of 500 mg. of chlortetracycline daily.

The patient in this instance was a 71-year-old white man who had bilateral pulmonary emphysema, extensive bronchiectasis, and cor pulmonale with chronic cardiac failure. During three months in the placebo series he had a persistent and distressing cough with associated dyspnea. Sleep became impossible. Vomiting occurred frequently in association with bouts of coughing; anorexia and weakness were marked. The 24-hour sputum exceeded 3 cupfuls (0.72 liter) and was yellow and thick; microscopic examination revealed innumerable polymorphonuclear leucocytes. After the patient's transfer to the antibiotic-treated group improvement was observed. Within seven days dyspnea was less marked, coughing was less frequent, and the sputum contained only moderate numbers of polymorphonuclear leucocytes. In addition, there was a progressive reduction in expectorated material. Subsequently, increased appetite and strength were observed; sleep again became possible.

Only 2 of the 21 persons in the group treated prophylactically with chlortetracycline required hospitalization during the course of this study (Table 2). The total

number of hospital days was 17. It became necessary, on the other hand, to hospitalize three of the nine control patients for a total of 34 days during this investigation. Objectively the incidence of respiratory infections was reduced more than 50% in the antibiotic-treated group as compared with the controls. Purulent sputum occurred quite rarely in those receiving antibiotic medication, as contrasted with its usual presence in the placebo group during the winter months. Perhaps the most striking manifestation of improvement in the chlortetracycline-treated patients was increased appetite, which was observed in eight cases. Only one person in the placebo group noted similar improvement. Increased strength, energy, and zest for life accompanied reduction in dyspnea and cough in the antibiotic-treated patients.

Each person in both categories was asked if he considered his health to have improved, to have remained unchanged, or to have become worse since the present study was begun (Table 3). In the chlortetracycline-treated series 17 considered themselves better, 3 thought there had been no change, and 1 regarded his health as

TABLE 2.—*Hospitalizations*

Series	Patients, No.	Hospitalizations, No.	Hospital Days/Patient
Chlortetracycline	21	2	8.5
Control	9	3	11.3

TABLE 3.—*Subjective Opinions of Patients After Prophylactic Therapy*

Series	Opinion		
	Better	No Change	Worse
Chlortetracycline	17	3	1
Control	3	2	4

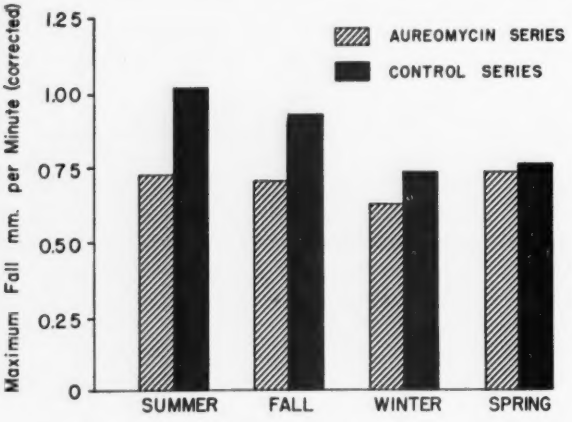
worse. Of the nine in the control series three thought themselves better, two had observed no change, and four believed themselves worse. The evaluation of subjective opinions is extremely difficult. However, the therapeutic method employed in this study was such that all patients believed themselves to be receiving the same medication. The examining physician was aware of what medication a given patient was receiving in only four instances. Furthermore, the long duration of this study should tend to obviate early psychological improvement.

Monthly sedimentation rates (Wintrobe, corrected) were persistently lower in the antibiotic-treated patients than in the controls (Chart). It is well to recall that the sedimentation rate tends to be higher in geriatric patients even in the absence of disease [17]; this is especially true if cardiovascular disease is present.[18] There was an average weight gain of 4.03 lb. (1.8 kg.) among the compensated patients in the aureomycin-treated group as compared with 2.4 lb. (1.1 kg.) in the untreated series

17. Wilhelm, W. F., and Tillisch, J. H.: Relation of Sedimentation Rate to Age, Med. Clin. North America **35**:1209, 1951.

18. Riseman, J. E. F., and Brown, M. G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, Am. J. M. Sc. **194**:392, 1937. Fredberg, A. S.; Blumgart, H. L.; Zoll, P. M., and Schlesinger, M. J.: Coronary Failure: The Clinical Syndrome of Cardiac Pain Intermediate Between Angina Pectoris and Acute Myocardial Infarction, J. A. M. A. **138**:107, 1948.

(Table 4). Evaluation of hematocrit determinations in chronic respiratory disease is rendered somewhat difficult by an occasional tendency toward compensatory polycythemia. It was recently reported that polycythemia rarely occurs with emphysema.[19] Possibly this is the result of malnutrition, inasmuch as the serum iron level is said to be depressed; again, this reduction in the concentration of serum iron in cases of emphysema may be caused by chronic bronchial infection.[20] It is a well-established clinical observation that anorexia and weight loss are typical of these persons. Only one patient in this study disclosed an abnormally elevated hematocrit determination (60%). This laboratory result was obtained shortly prior to death in the single fatal case in the antibiotic-treated group. This patient had diffuse emphysema and extensive bronchiectasis. Another person, in the control series, had a hematocrit level



Serial sedimentation rates in chronic pulmonary disease.

TABLE 4.—*Hematocrit and Wright Determinations*

Series	Hematocrit Level, Av. Increase, %	Weight, Av. Increase, Kg.
Chlortetracycline	2.6	1.8
Control	—0.8	1.1

above 50% (54%). The range in the remaining 28 subjects was 32 to 49%. Omitting from consideration the cases of polycythemia, an average increase was observed in the hematocrit level in the treated patients of 2.6%, as contrasted with an actual average decrease of 0.8% in the controls (Table 4). It is believed that this reflects an improved state of nutrition together with a reduction of bronchial infection in the chlortetracycline-treated patients.

Illustrative Case Reports.—Four cases are briefly summarized as examples of prolonged chlortetracycline therapy in chronic respiratory diseases.

19. Wilson, R. H.; Borden, C. W., and Ebert, R. V.: Adaptation to Anoxia in Chronic Pulmonary Emphysema, A. M. A. Arch. Int. Med. **88**:581, 1951.

20. Cartwright, G. E.; Lauritsen, M. A.; Jones, P. J.; Merrill, I. M. and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients, J. Clin. Invest. **25**:65, 1946. Wilson, Borden, and Ebert.[19]

CASE 1.—M. S., a 64-year-old white woman, had suffered from repeated severe bouts of bronchial asthma for 27 years. For approximately six years persistent dyspnea had been present even at rest; cough was almost constant, with exacerbations resulting from changes in position or attempts at conversation; sputum amounted to approximately 2 cupfuls (0.48 liter) every 24 hours. Extreme anorexia, progressive weight loss, weakness, and malaise had been present for several years. The weight had declined to 79 lb. (35.5 kg.). Since 1939 frequent respiratory infections had occurred each fall, winter, and early spring. Bronchopneumonia had necessitated four periods of hospitalization at the John Gaston Hospital during the two and one-half years immediately prior to this study. On Sept. 4, 1951, after the diagnosis of chronic bronchitis, bronchial asthma, pulmonary emphysema, and bronchiectasis had been established, therapy was begun with 500 mg. of chlortetracycline daily. During the 20 months this patient was observed, no hospitalization was necessary. Respiratory infections were reduced approximately 70%; cough became much less frequent and sputum was decreased 60 to 70%. Body weight increased from 79 to 86 lb. (35.5 to 38.7 kg.). In addition, the hematocrit level rose from 45 to 47.5% and vital capacity increased from 1.6 to 1.8 liters. A sternal marrow examination was performed after one year of therapy; no evidence of toxicity was demonstrated.

Perhaps the most satisfying result of prophylactic treatment in this case, however, was the improved attitude of the patient. For the first time in four years she was able to do her own washing and, for the first time in five years, needed no assistance in carrying on her housework. Furthermore, she was now able to attend public functions and thereby extend her circle of interests. It should be noted that the previous therapeutic regimen was continued. This consisted of frequent postural drainage, use of expectorants and bronchial dilators, and adequate diet and vitamin supplements.

CASE 2.—B. J. S., a 13-year-old white boy, was admitted to the antibiotic prophylactic study on Oct. 11, 1951. Between 1945 and 1949 this patient had been repeatedly hospitalized for acute bronchitis and bronchopneumonia. Because of anemia and failure to maintain his weight, various iron preparations and innumerable vitamin supplements had been administered through the outpatient department and by many private physicians. Nonetheless, the child had continued to complain of extreme fatigue, anorexia, and malaise. Occasional fainting spells occurred in association with bouts of coughing. For three years he was regarded as a behavior problem and was under the care of a psychiatrist.

Finally, in April 1949, bronchograms established the diagnosis of bronchiectasis of the lower lobe of the left lung. Surgical resection was carried out, with the pathologic report being acute bronchiectasis and acute lung abscess. Convalescence was not complicated. However, from April 1949 until the present study was instituted, two episodes of bronchopneumonia necessitated hospitalization. Also, repeated courses of antibiotic therapy were administered through the outpatient department and the receiving ward of the John Gaston Hospital for recurrent respiratory infections. Bronchograms, in October 1951, disclosed extensive bronchiectatic involvement of the lower lobe of the right lung. Further surgery, however, was refused by the patient's family. Therefore, he was referred to the antibiotic clinic for chlortetracycline treatment.

During 18 months of chlortetracycline prophylactic therapy, the appetite increased, pulmonary infections were reduced more than 70%, and no episode of bronchopneumonia occurred. Not a single period of fever was noted, and hospitalization was not necessary. No toxic effects to treatment were observed. There was an increase in body weight of 21 lb. (9.4 kg.), from 73 to 94 lb. (32.8 to 42.3 kg.); the vital capacity improved, from 3.0 to 3.4 liters, and the hematocrit level rose from 37 to 44%. Additional treatment consisted of postural drainage, expectorants, and adequate diet.

CASE 3.—M. C., a 46-year-old white woman, was admitted to the chlortetracycline prophylactic series on Jan. 15, 1952, at the request of the otolaryngology service of the John Gaston Hospital and the University of Tennessee College of Medicine.

This patient had been hospitalized initially on Jan. 24, 1949, because of acute suppurative otitis media and pneumococcic meningitis. After three weeks of treatment with sulfadiazine and penicillin, she was discharged without sequelae. The following year (Dec. 27, 1950) she was once more hospitalized, in a comatose condition with acute otitis media and pneumococcic meningitis. Again, therapy consisted of 1,600,000 units of parenterally administered penicillin daily with sulfadiazine in dosage of 4 gm. on admission and then 1 gm. orally every four hours. On

this occasion, hospitalization required four and one-half weeks. No neurologic complications developed. Three months later, further hospitalization was necessary because of chronic sinusitis, chronic otitis media, and acute bronchitis. An excellent clinical response was obtained in four days with 50,000 units of parenterally administered penicillin every three hours. The fourth admission to John Gaston Hospital occurred on Dec. 25, 1951, because of meningitis and associated acute otitis media and acute sinusitis. Organisms identified as Group B Hemophilus influenzae were isolated from the spinal fluid. After a stormy course of four weeks, during which she received massive amounts of chloramphenicol, streptomycin, sulfadiazine and penicillin, the patient was discharged to be observed through the outpatient department.

Two weeks after the patient left the hospital (Jan. 15, 1952), chlortetracycline prophylactic treatment was begun, using 500 mg. daily. During the ensuing 15½ months no significant respiratory infection occurred; only a minimal episode of pharyngitis was present for three days. This was the first winter in four years that meningitis did not occur. Because of increased appetite and subsequent weight gain, it became necessary for the patient to adopt a reduction diet. Of interest was the fact that the hematocrit level increased from 42 to 45%. No toxic side effects to therapy were observed.

Case 4.—E. K., a 62-year-old white woman, had been unable to support herself since 1947 because of severe dyspnea on exertion, constant productive cough, weakness, marked weight loss, multiple episodes of profuse bloody diarrhea, and repeated bouts of respiratory infections. A diagnosis of chronic bronchitis, hypertrophic pulmonary emphysema, and bilateral bronchiectasis had been established in a neighboring city in 1945. In 1947 bronchograms disclosed bronchiectasis involvement of the middle and lower lobes of the right lung as well as the lower lobe of the left lung. The following year clinical findings together with sigmoidoscopic and roentgenologic examinations at the John Gaston Hospital confirmed the existence of chronic idiopathic ulcerative colitis.

On Sept. 24, 1952, this patient was admitted to the chlortetracycline-treated series. While improvement was not dramatic, it was progressive. During the winter of 1952-1953 no serious respiratory infection occurred; according to the patient the cough was better than it had been in five years. Sputum was reduced approximately 60%. For the first time in three years, this patient began attending public gatherings such as church and motion pictures. Dyspnea became less marked, appetite increased, and the patient noted a definite increase in energy. Furthermore, only one episode of bloody diarrhea occurred during the seven months of observation. Following the institution of antibiotic treatment, weight increased from 80.5 to 82 lb. (36.2 to 36.9 kg.) and monthly sedimentation rates (Wintrobe, corrected) were persistently within normal limits. Recent sigmoidoscopic and roentgenoglogic examinations disclosed striking improvement in the status of the ulcerative colitis.

Toxicity.—Toxic side effects of the prolonged administration of chlortetracycline were quite minimal. In only one instance was it necessary to discontinue medication. This was for a 65-year-old white woman who had chronic bronchitis, bilateral bronchiectasis, and diffuse pulmonary fibrosis. Three days after chlortetracycline therapy was begun a severe painless diarrhea developed. This was characterized by 8 to 10 daily semiliquid stools containing streaks of blood; there was no associated nausea or vomiting. Weakness, anorexia, and malaise became pronounced. Antispasmodics and mild sedatives were administered. After two days chlortetracycline was reduced to 100 mg. twice a day. However, only slight improvement was observed. Therefore, the patient was transferred to the control group and use of chlortetracycline was discontinued. Within 72 hours bowel movements were normal as to number and consistency. No further blood was observed. During the ensuing three months two episodes of acute bronchitis occurred.

Table 5 represents the untoward effects of therapy observed in this investigation. Diarrhea, pruritus ani, and pruritus vulvae occurred only in the antibotic series. One patient in the chlortetracycline-treated group who had transient and moderate diarrhea also suffered from chronic idiopathic ulcerative colitis (Case 4). Definite clini-

cal, sigmoidoscopic, and roentgenologic improvement in the chronic intestinal disease was observed in this instance. Likewise, respiratory complaints were significantly reduced. While pruritus ani occurred twice among those who received chlortetracycline, it was mild in both instances. In one patient it was noted after 10 weeks of treatment and persisted for three days; in the other it developed after 8 months and was present for a week. Only symptomatic therapy was employed in either instance. All patient were instructed to practice strict hygienic measures, with great caution being observed to avoid anal irritation.

Although comprehensive liver function tests were performed regularly, no evidence of hepatic toxicity was observed. Indeed, laboratory studies revealed several examples of improved function in the chlortetracycline-treated series: in two instances cholesterol esters increased from 46 and 59% to 82 and 77%, respectively; in one case, a 3+ (at 24 hours) cephalin-cholesterol flocculation determination became negative, while in another person the sulfobromophthalein retention (5 mg. per kilogram after 45 minutes) decreased from 5 to 2.5+. The only abnormality which

TABLE 5.—*Side Effects of Prophylactic Chlortetracycline Therapy*

	Series	
	Chlortetracycline	Control
Nausea	0	1
Vomiting	0	1
Diarrhea		
Mild	1	0
Moderate	2	0
Severe	1	0
Constipation	2	1
Pruritus ani	2	0
Pruritus vulvae	1	0
Ptyalism	1	0
Indigestion (heartburn)	1	0
Anorexia	1	1

developed during chlortetracycline treatment consisted of an increase in sulfobromophthalein retention from 5 to 10%. The one significant alteration in the control group was an increase in the sulfobromophthalein retention from less than 5 to 15% in one patient. Bone marrow studies were performed in 14 cases; no evidence of toxicity was revealed.

Bacteriologic and In Vitro Sensitivity Studies.—From April 1, 1953, through April 30, 1953, sputum specimens were collected from 14 patients in the chlortetracycline-treated group and 9 in the control group. Two specimens were obtained at an interval of three weeks from one person in the placebo group, thus making a total of 10 control specimens. Each preparation was examined microscopically for the presence of polymorphonuclear leucocytes. In addition, every specimen was cultured aerobically within an hour of its collection on both blood agar and eosin-methylene blue (Difco) plates. The tube dilution method was employed to determine the sensitivity of bacteria to chlortetracycline.

Only 1 of the 14 specimens from the antibiotic-treated patients disclosed more than 10 polymorphonuclear leucocytes microscopically per high-power field, as contrasted to 3 of the 10 control preparations. The bacterial flora and the incidence of Candida albicans in the two groups are presented in Table 6. C. albicans was isolated

from 4 of 14 patients in the chlortetracycline-treated group as compared with 3 in the placebo series. It would appear that the methyl and propyl esters of *p*-hydroxybenzoic acid (Paraben) are capable of preventing the overgrowth of Candida associated with chlortetracycline therapy. M. pyogenes var. aureus and nonhemolytic streptococci occurred more frequently in the control group than in the antibiotic series. Of special interest is the fact that three of the five hemolytic strains of M. pyogenes var. aureus were isolated from patients receiving placebo medication. The potential danger of

TABLE 6.—*Sputum Flora in Chlortetracycline-Treated and Control Patients*

	Specimens with Microorganisms, No.	
	Chlortetracycline Series (14 Specimens)	Control Series (10 Specimens)
Esch. coli	4	1
A. aerogenes	5	0
P. vulgaris	2	0
Ps. aeruginosa	1	1
Str. fecalis	1	0
Str. viridans type	12	7
Nonhemolytic streptococci	3	6
Hemolytic streptococci	2	2
M. pyogenes aureus	3 (2 hemolytic strains)	5 (3 hemolytic strains)
M. pyogenes albus	0	1
Pneumococci	2	3
Neisseria species	7	5
C. albicans	4	3

TABLE 7.—*In Vitro Sensitivity Studies*

	Concentration Required for Inhibition, Chlortetracycline/Cc. of Medium					
Series	Esch. Coli	A. Aerogenes	P. Vulgaris	Ps. Aeruginosa	M. Pyogenes Aureus	Neisseria Species
Chlortetracycline	8.00	2.00	16.00	1.00	2.00	2.00
	2.00	1.00	1.00	....	2.00	1.00
	1.00	5.00	....	....	0.50	0.25
	0.50	0.50	....	....	....	0.25
	....	0.25	....	....	....	0.25
	....	....	....	....	....	0.12
Control	0.25	....	....	4.00	2.00	0.25
	....	....	....	....	0.25	0.25
	....	....	....	....	0.25	0.12
	....	....	....	....	0.25	0.12
	....	....	....	....	0.12	0.12

these organisms in broad spectrum antibiotic therapy has been repeatedly emphasized in the current literature. Aerobacter aerogenes and Escherichia coli occurred much more frequently in those receiving chlortetracycline than in the controls.

Sensitivity studies (Table 7) disclosed no evidence of the development of significant resistance of hemolytic or nonhemolytic strains of M. pyogenes var. aureus.[21] Likewise, no definite increase in resistance was demonstrated in strains of Esch. coli,

21. Karel, L., and Roach, E. S.: A Dictionary of Antibiosis, New York, Columbia University Press, 1951. Paine, T. F., Jr.; Collins, H. S., and Finland, M.: Laboratory Studies with Aureomycin, Ann. New York Acad. Sc. **51**:228, 1948.

Ps. aeruginosa, or P. vulgaris.[21] While A. aerogenes was obtained only from cases in the antibiotic-treated group, all five strains of this organism were quite sensitive to chlortetracycline.

COMMENT

With the increasing age of the general population, nontuberculous chronic respiratory diseases such as chronic bronchitis, hypertrophic pulmonary emphysema, and bronchiectasis are becoming increasingly important. There is no more distressing clinical picture than that produced by extensive forms of these conditions. Dyspnea even at rest, persistent cough, anorexia, weakness, weight loss to the point of emaciation, anemia and malnutrition, malaise and mental apathy are the cardinal clinical manifestations. Pulmonary heart disease, cor pulmonale, is common and adds to this disabling syndrome. As a result of respiratory insufficiency, employment is rarely feasible; because of persistent annoying cough, the presence of these persons is usually distasteful. Therefore, these persons are both economic and psychiatric problems.

Until recently nontuberculous chronic pulmonary diseases were regarded as hopeless. Diagnosis was possible; effective therapy was nil. However, improvement has been obtained by combined use of frequent postural drainage, respiratory exercises, abdominal supports, expectorants, bronchodilators, and adequate diet. Nevertheless, anorexia with resultant malnutrition and cachexia remains a challenge to therapy. Furthermore, intercurrent respiratory infections continue to constitute the principal hazard to the survival of these elderly persons. Patients with chronic pulmonic disease are extremely susceptible to secondary or superimposed respiratory disease. Unfortunately such infections are quite dangerous to these persons because they have a very narrow margin of pulmonary reserve. Even a minimal episode of acute bronchitis may be sufficient to cause abrupt respiratory insufficiency and death. If the latter does not result, hospitalization with prolonged invalidism and economic loss is common.

Present-day treatment has been directed primarily at the prompt and adequate management of respiratory infections. For this purpose, sulfadiazine, penicillin, streptomycin, and the broad spectrum antibiotics have been quite effective for short-term use. Unfortunately, it is often difficult to diagnose an intercurrent respiratory infection in persons having chronic pulmonary disease. There may be little alteration in cough, no increase in chest pain, and little or no fever or leucocytosis. Nonetheless, serious results may rapidly ensue if adequate therapy is not promptly instituted.

We believed that the most promising management of intercurrent infections in cases of chronic respiratory disease would be the actual prevention of these episodes. Inasmuch as chlortetracycline is an effective agent against many Gram-positive and Gram-negative organisms, it was decided to investigate the prophylactic action of this antibiotic. Therefore, 21 persons were given 500 mg. of chloretetracycline daily for an average of 11 months, while 9 similar persons received placebo material identical in appearance. Both groups of cases were then compared by clinical and laboratory methods. A single death occurred in each group. However, the fatality in the antibiotic series was not related to an intercurrent infection. Necropsy in this instance revealed no evidence of an acute inflammatory process. On the other hand, the death in the control category resulted from bronchopneumonia. The

incidence of respiratory infections was reduced by more than 50% in the chlortetracycline-treated patients as compared with the control subjects. As a consequence, only 2 of 21 persons receiving prophylactic antibiotic therapy required hospitalization, as contrasted to 3 out of 9 in the placebo series. This represents a significant economic advantage.

Subjective improvement was much more marked in the antibiotic group than in the placebo group. The validity of these views was strengthened by the experimental methods employed in this investigation. Of greatest importance, however, was the fact that subjective reports were supported by objective and laboratory results. Greater weight gains, increased hematocrit determinations, and persistently lower sedimentation rates were observed in the antibiotic-treated group as compared with the controls. Improved appetite with increased energy and zest for life was a striking occurrence in many of the chlortetracycline-treated patients. Several were able to resume social activities for the first time in several years.

With the dosage employed in this study, side effects to treatment were minimal. In only one instance was it necessary to discontinue therapy because of toxicity. In this case severe painless diarrhea developed shortly after treatment was begun; this persisted despite the reduction of chlortetracycline from 500 mg. to 200 mg. daily. Diarrhea, pruritus ani, and pruritus vulvae occurred only in those receiving chlortetracycline; however, these complications were few, mild, and transient. No instances of glossitis or sore mouth were observed.

Comprehensive sputum studies revealed no evidence of overgrowth by resistent organisms such as Ps. aeruginosa, P. vulgaris, hemolytic strains of Micrococcus pyogenes var. aureus, or C. albicans. The addition of the methyl and propyl esters of *p*-hydroxybenzoic acid to chlortetracycline is effective in preventing the proliferation of yeast. It should be noted that the dosage of chlortetracycline was increased in two cases in the antibiotic-treated group from 500 mg. to 1 gm. daily for five to seven days because of intercurrent infections (axillary abscess and acute bronchitis). Excellent results were obtained in both instances. In vitro sensitivity studies employing organisms isolated from the sputum of these patients revealed no evidence of the development of significant resistance to chlortetracycline.

It appears that 500 mg. of chlortetracycline daily are able to forestall many infections by common Gram-positive and Gram-negative respiratory pathogens. However, such dosage does not alter the bacterial flora to such a degree that resistant organisms as Ps. aeruginosa and P. vulgaris are able to thrive in an unlimited manner.

The present studies indicate that the prolonged administration of chlortetracycline as a prophylactic agent may be of definite value in certain chronic respiratory diseases. Further observations are necessary to evaluate more completely the question of bacterial resistance. Likewise, it is not suggested that the optimal dosage of chlortetracycline for prophylactic purpose has been established.

SUMMARY

The long-term use of broad-spectrum antibiotics may not only be feasible, but, indeed, may be quite valuable. While further investigation is necessary, bacterial resistance does not appear to constitute a serious problem to prolonged chlortetracycline treatment. It is hoped that the present studies may provide a new and valuable approach to antibiotic therapy.

ELECTROLYTE, WATER, AND MERCURY EXCRETION AFTER ORAL ADMINISTRATION OF NEOHYDRIN

Observations on Experimental Use of Neohydrin (1347EX), a Chloro Derivative, and Two Thiol (1353EX and 1431EX) Derivatives of 2-Methoxy-Propylurea

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ALTHOUGH mercurials exhibit diuretic properties when given orally,[1] the diuresis produced has generally been considered to be inadequate and inferior to that obtained following use of the parenteral route,[2] and for this reason the oral route of administration has not been very popular. However, several recently synthesized mercurial diuretics have been shown to exhibit greater diuretic potency than meralluride (Mercuhydrin).[3] With the development of more active compounds it seemed worth while to investigate the diuretic potential of these three experimental mercurials when administered by the oral route. The three compounds under investigation are (1) Neohydrin (3-chloromercuri-2-methoxypropylurea [1347Ex]), (2) 3-carboxymethyl-mercaptomercuri-2-methoxypropylurea (1353 Ex), and (3) 3-(*a*-carboxyethylmercaptomercuri)-2-methylpropylurea (1431Ex). Observations were made on the effect of oral administration of these compounds on water and electrolyte excretion in both normal subjects and in patients with cardiac failure. In addition, mercury excretion studies were performed on patients and on dogs.

METHODS AND MATERIALS

Clinical observations were made on mercury, electrolyte, and water excretion. Pilot studies were performed for 18 normal ambulatory subjects who were on a relatively constant but not on a low sodium intake. Three of the subjects were given doses of each of the diuretics equivalent to 40 mg. Hg (4 tablets) and three were given doses equivalent to 60 mg. Hg

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1. (*a*) Dickens, K. L.: Oral Administration of Mercurial Diuretics in the Treatment of Congestive Heart Failure, New Orleans M. & S. J. **94**:344, 1942. (*b*) Batterman, R. C.; DeGraff, A. C., and McCormack, J. E.: The Effectiveness and Safety of Mercupurin Administered Orally in the Treatment of Congestive Heart Failure, J. A. M. A. **124**:1243, 1944.

2. Batterman, R. C.; DeGraff, A. C., and Shoss, H. M.: Further Observations on the Use of Mercupurin Administered Orally, Am. Heart J. **31**:431, 1946. Dickens.[1a]

3. Handley, C. A.; Chapman, D. W., and Moyer, J. H.: Some Pharmacological Properties of Three New Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **78**:433, 1951.

(6 tablets). Thus, six subjects received each diuretic, three getting 40 mg. Hg per day and three getting 60 mg. Hg. per day. Before the drug was given, urine was collected for three to five successive 24-hour control periods. Then the experimental diuretics were administered in four divided doses (with each meal and at bedtime) each day for five to seven days. The urine was collected for successive 24-hour periods. The control values in Tables 1 and 2 are the average observations during the three to five control days, and the values are for the period of drug administration, the averages of the five to seven days during which the patients were receiving the experimental diuretics. All urine was analyzed for sodium and potassium, using the Beckman flame photometer. Random urine samples were analyzed for mercury excretion, using the dithizone method of mercury analysis.

Similar studies were done on 26 patients with heart failure who were ambulatory but who were in the hospital. From the observations on the normal subjects (Table 1) it appeared that none of the diuretics had much effect on sodium and water excretion in dosages of less than 60 mg. Hg (6 tablets). Therefore, when the patients in heart failure were studied doses were used which contained 60 to 80 mg. Hg (6 to 8 tablets) per 24 hours for each of the three experimental diuretics. Because of the apparent greater potency of Neohydrin, three patients also received a dose of this drug in amounts equivalent to 40 mg. Hg (4 tablets) per 24 hours. Most of the patients with heart failure were on a low-sodium diet. The methods of drug administration and the methods for studying electrolyte, water, and mercury excretion of the patients with heart failure were similar to the methods employed for the normal subjects. The observations made after the diuretic was given, presented in Tables 1 and 2, are the average values for five to seven 24-hour periods. During the initial observations on both the normal subjects and the patients with heart failure it became evident that Neohydrin (1347Ex) was the most potent diuretic of the three experimental drugs being studied. Therefore, a greater number of patients taking this drug were studied in more detail. Seriously ill patients were not included, since adequate control observations (at least three successive 24-hour collection periods) could not have been made before administering the diuretics. Prior to treatment all of the patients had peripheral edema of a moderate degree and most of them had collateral evidence of congestive heart failure, such as pulmonary rales, dyspnea, and hepatomegaly.

Laboratory observations were made on fecal and urinary excretion of mercury and the residual tissue content after the oral administration of a single dose of Neohydrin (1347Ex) tablets to dogs. A single dose of six tablets of Neohydrin, containing a total of 60 mg. Hg, was administered to each of 10 dogs. After the drug was administered, urine and feces were collected in successive 24-hour intervals and analyzed for mercury content. The entire fecal specimen was mixed with an equivalent weight of N/10 H_2SO_4 and blended thoroughly before samples were removed for analysis. After the collection of the seventh 24-hour specimens the animals were killed, and samples of heart, liver, kidney, spleen, brain, ovaries, and pancreas were analyzed for mercury content.

Clinical Observations.—The clinical observations on water and electrolyte excretion following administration of each of the experimental diuretics are summarized in Table 1. Consistent changes were not observed in potassium excretion with any of the drugs, regardless of the dosage schedules used. However, following administration of Neohydrin there was a trend toward increased potassium excretion in several of the patients in heart failure (Chart 3). In the pilot studies on normal persons none of the diuretics appeared to increase sodium excretion in doses equivalent to 40 mg. Hg (4 tablets), but in all of them there was some response to 60 mg. Hg (6 tablets) per day. The absolute increase in sodium excretion in the subjects receiving 60 mg. Hg was most marked in those receiving Neohydrin, but the effect on water excretion was not as prominent. This may have been due to some variability in physical activity among the different subjects.

When Neohydrin (1347Ex) was administered in doses of 40 mg. Hg (4 tablets) to patients in heart failure, there was an increase in sodium excretion but not in water excretion. When doses containing 60 and 80 mg. Hg (6 to 8 tablets) per day were given, the increase in sodium excretion was considerably greater follow-

TABLE 1.—*Comparison of Water and Electrolyte Excretion Using Three Experimental Diuretics Administered Orally in Different Doses to Normal Subjects and Patients in Heart Failure (Average Values)*

	Patients, No.	Dose, Mg. Hg *	Sodium Excretion † C	Sodium Excretion † D	Sodium Excretion † Inc.	Sodium Excretion † % Inc.‡	Potassium Excretion † C	Potassium Excretion † D	Potassium Excretion † Inc.‡	Water Excretion † C	Water Excretion † D	Water Excretion † Inc.	Water Excretion † % Inc.‡	Mercury Excretion Mg. Hg/24 Hr.	Mercury Excretion % of Intake
Response to 1353Ex															
Normal	3	40	1.53	1.68	0.15	10	0.89	1.64	0.75	795	973	178	22	2.04	5.1
Normal	3	60	1.42	1.93	0.51	36	0.84	0.90	0.06	938	1040	102	11	....	...
C. F.§	3	60	1.10	1.64	0.54	49	2.32	2.23	—0.09	1130	1323	193	17	....	...
C. F.	3	80	0.76	1.37	0.61	80	1.47	1.46	—0.01	1300	1717	417	32	....	...
Response to 1431Ex															
Normal	3	40	4.01	4.10	0.09	2	3.13	3.48	0.35	1759	1859	100	6	2.24	5.6
Normal	3	60	3.22	3.81	0.59	18	2.23	1.96	—0.27	1483	1831	348	23	3.99	6.7
C. F.	7	80	1.48	2.26	0.78	53	1.31	1.26	—0.05	1057	1582	525‖	50	4.70	5.9
Response to Neohydrin (1347Ex)															
Normal	3	40	4.53	4.42	—0.10	— 2	2.98	2.47	—0.50	1636	1765	129	8	3.92	9.8
C. F.	3	40	0.88	2.31	1.44	164	1.65	1.84	0.19	3307	3397	90	3	3.81	9.5
Normal	3	60	3.56	4.87	1.30	37	2.06	2.04	—0.01	1556	1723	167	11	4.94	8.2
C. F.	3	60	1.58	3.85	2.27	144	1.86	1.76	—0.10	1732	2285	553	32	5.48	9.1
C. F.	10	80	0.99	4.19	3.20¶	323	1.32	1.42	0.10	1285	2563	1278‖	99	6.78	8.5

* Diuretic containing this amount of mercury was given over a 24-hour period.
† Sodium and potassium excretion is in grams per 24 hours. Water excretion is in cubic centimeters per 24 hours. C = control (average of three to five days). D = after diuretic was started (average of five to seven days).
‡ % Inc. = average increase of individual observations.
§ C. F. = cardiac failure.
‖ Statistically significant, $P < 0.05$.
¶ Statistically significant, $P < 0.01$.

TABLE 2.—*Changes in Water and Electrolyte Excretion Following Oral Administration of Neohydrin (1347Ex) to Normal Subjects and Patients in Heart Failure*

Patient	Diagnosis	Drug	Dose,* Mg./Kg.	Sodium Excretion † C	Sodium Excretion † E	Sodium Excretion † Inc.	Potassium Excretion † C	Potassium Excretion † E	Potassium Excretion † Inc.	Urine Volume † C	Urine Volume † E	Urine Volume † Inc.	Hg Urine, Mg.‡
Ha.....	Normal	1347	40	3.62	3.78	0.16	2.94	3.10	0.16	1800	1750	— 50	....
Mo.....	Normal	1347	40	5.11	4.50	—0.61	2.64	1.60	—1.04	1918	2350	432	4.77
Su.....	Normal	1347	40	4.85	4.99	0.14	3.35	2.72	—0.63	1190	1195	5	3.07
Mean for normal subjects.....			40	4.53	4.42	—0.10	2.98	2.47	—0.50	1636	1765	129	3.92
Rg.....	ASHD	1347	40	1.68	3.85	2.17	1.72	1.96	0.24	3360	4000	640	....
Je.....	ASHD	1347	40	0.72	0.74	0.02	1.12	1.24	0.12	3150	3030	—120	3.81
As.....	ASHD	1347	40	0.23	2.35	2.12	2.10	2.32	0.22	3410	3160	—250	....
Mean			40	0.88	2.31	1.44	1.65	1.84	0.19	3307	3397	90	3.81
Mo.....	Normal	1347	60	4.05	4.29	0.24	2.52	1.89	—0.63	2114	2128	14	4.13
Ha.....	Normal	1347	60	3.58	5.96	2.38	2.26	2.65	0.39	1646	1855	209	4.80
Le.....	Normal	1347	60	3.06	4.35	1.29	1.39	1.59	0.20	908	1185	277	5.90
Mean for normal subjects.....			60	3.56	4.87	1.30	2.06	2.04	—0.01	1556	1723	167	4.94
Ga.....	ASHD	1347	60	1.36	5.04	3.68	2.32	1.32	—1.00	1522	2267	745	6.32
Tg.....	HCVD	1347	60	2.40	4.54	2.14	1.97	1.75	—0.22	2075	2469	394	4.77
Os.....	HCVD	1347	60	0.98	1.96	0.98	1.28	2.20	0.92	1600	2120	520	5.36
Mean for patients with cardiac disease			60	1.58	3.85	2.27	1.86	1.76	—0.10	1732	2285	553	5.48
Ga.....	ASHD	1347	80	1.36	7.40	6.04	2.32	2.05	—0.27	1522	2983	1461	6.79
Os.....	HCVD	1347	80	2.40	4.51	2.11	1.97	2.32	0.35	2075	2563	488	5.78
Be.....	HCVD	1347	80	1.73	3.43	1.70	1.05	0.29	—0.76	1090	1583	493	....
Pa.....	?	1347	80	0.93	2.84	1.91	1.93	2.52	0.59	2133	5965	3832	....
Ja.....	RHD	1347	80	0.20	0.72	0.52	0.33	0.75	0.42	365	802	437	....
Da.....	ASHD	1347	80	0.15	5.32	5.17	1.07	1.68	0.61	530	2315	1785	7.94
McH.....	HCVD	1347	80	0.90	3.70	2.80	0.64	1.45	0.81	1050	2265	1215	....
Bo.....	HCVD	1347	80	0.52	5.89	5.37	0.81	0.68	—0.13	755	2835	2080	6.54
Ma.....	RHD	1347	80	0.78	3.26	2.48	0.79	0.98	0.19	1440	2230	790	....
Ogr.....	ASHD	1347	80	0.90	4.80	3.90	2.32	1.51	—0.81	1899	2080	200	6.86
Mean			80	0.99	4.19§	3.20	1.32	1.42	0.10	1285	2563 ‖	1278	6.78

* Milligrams of mercury contained in the daily dose of the experimental diuretic.
† Sodium excretion expressed in grams per 24 hours; potassium excretion expressed in grams per 24 hours; water excretion (urine volume) expressed in cubic centimeters per 24 hours. C = control; E = after drug; Inc. = increase in excretion.
‡ Mercury excretion in urine expressed in mg. per 24 hours.
§ Statistically significant, $P < 0.01$.
‖ Statistically significant, $P < 0.05$.

TABLE 3.—*Electrolyte, Water, and Mercury Excretion (Before and After Neohydrin and 1431Ex) in a Normal Subject and a Patient with Mild Heart Failure*

Subject C. A. H. (Normal) 6 Tablets per Day 60 Mg. of Hg						Subject C. L. (Mild Cardiac Failure) 6 Tablets per Day 60 Mg. of Hg					
Day	Drug	Urine Vol., Ml.*	Na, Gm.*	K, Gm.*	Hg, Mg.*	Day	Drug	Urine Vol., Ml.*	Na, Gm.*	K, Gm.*	Hg, Mg.*
1	Control	1715	2.97	2.04	....	1	Control	775	3.76	1.47	....
2	Control	1860	3.48	2.97	....	2	Control	975	3.85	1.48	....
3	Control	1710	2.98	1.71	....	3	Control	890	2.15	1.35	....
4	Control	1300	3.88	2.31	....	Mean (control)		880	3.25	1.43	....
Mean (control)		1646	3.33	2.26	....	4	1431Ex	870	4.04	0.92	1.45
5	1347Ex †	2720	8.95	3.54	3.95	5	1431Ex	850	3.33	1.40	1.72
6	1347Ex	1200	6.00	2.30	4.93	6	1431Ex	970	3.34	1.58	2.30
7	1347Ex	1520	6.50	2.80	5.42	7	1431Ex	1285	4.51	1.11	2.15
8	1347Ex	1760	6.17	2.94	4.20	8	1431Ex	1315	3.34	1.38	2.52
9	1347Ex	1900	5.50	2.42	5.10	9	1431Ex	1340	5.95	1.74	2.58
10	1347Ex	1930	2.66	1.92	3.20	10	1431Ex	1200	5.89	1.20	2.84
Mean (after drug)		1838	5.96	2.65	4.47	Mean (after drug)		1119	4.34	1.33	2.22
13	None	1160	4.76	3.36	....	14	None	840	3.54	1.30	....
14	None	1150	2.82	1.68	0.00	15	None	740	2.21	1.55	....
15	None	1290	3.25	2.06	....	16	None	970	2.85	1.47	....
Mean (control)		1200	3.61	2.37	....	Mean (control)		850	2.87	1.44	....
16	1431Ex	2050	4.51	2.15	1.96	17	1347Ex †	1100	4.53	1.83	2.86
17	1431Ex	1380	4.30	2.26	3.12	18	1347Ex	1300	5.65	1.17	7.94
18	1431Ex	2300	2.30	0.97	2.48	19	1347Ex	1120	4.40	1.16	5.15
19	1431Ex	2100	4.09	2.52	4.45	20	1347Ex	1150	4.15	1.78	5.75
20	1431Ex	1240	9.30	3.21	4.40	21	1347Ex	1150	5.40	2.05	6.44
21	1431Ex	1500	5.25	2.29	4.61	22	1347Ex	880	3.96	1.43	6.66
22	1431Ex	2350	4.96	2.36	2.64	23	1347Ex	890	3.56	1.51	6.48
Mean (after drug)		1846	4.96	2.25	3.38	24	1347Ex	1890	3.16	1.76	....
						Mean (after drug)		1185	4.35	1.59	5.90

* Per 24 hours.
† Neohydrin.

TABLE 4.—*Mercury Excretion in Urine and Feces Following Oral Administration of Neohydrin in a Single Dose Containing 60 Mg. Hg*

	Mercury in Urine, Mg.						Mercury in Feces, Mg.							
	Time After Ingestion, Hr.				Total "Absorbed"*		Time After Ingestion, Hr.						Total Hg Recovered †	
Dog No.	24	48	72	96	Mg.	%	24	48	72	96	120	144	Mg.	%
1	3.60	0.52	0.00	0.00	4.12	7	44.00	1.65	0.15	0.04	0.00	0.00	49.96	83
2	4.33	1.20	0.20	0.12	5.85	10	4.50	41.22	3.42	2.00	0.66	0.34	57.99	97
3	2.24	0.10	0.14	0.00	2.48	4	12.92	24.20	0.71	0.20	0.07	0.02	40.60	68
4	4.93	0.76	0.10	0.00	5.79	10	40.25	2.03	1.12	0.21	0.00	0.00	49.40	82
5	2.88	0.51	0.25	0.00	3.64	6	38.21	10.00	2.13	0.30	0.00	0.00	54.28	90
6	1.78	1.34	0.00	0.00	3.12	5	34.20	0.00	5.00	....	0.48	0.00	42.80	71
7	1.35	3.22	0.23	0.00	4.80	8	45.10	4.91	0.89	0.51	0.32	0.02	56.55	94
8	2.60	1.23	0.00	0.00	3.83	6	35.11	7.80	0.41	0.15	0.11	0.00	47.41	79
9	2.10	0.38	0.11	0.00	2.59	4	31.20	10.25	0.34	0.08	0.03	0.00	44.49	74
10	4.32	0.13	0.03	0.00	4.48	7	41.30	2.64	0.26	0.15	0.05	0.00	48.88	81
Mean	3.01	0.94	0.12	0.01	4.07	7	32.68	10.47	1.44	0.40	0.17	0.04	49.24	82

* Previous observations indicate that 90% of diuretic administered intravenously is excreted in the urine.
† Total recovered in urine and feces expressed in percent of amount ingested.

ing Neohydrin than following 1431Ex and 1353Ex. Although in absolute values there did not appear to be much difference in sodium excretion between 60 mg. Hg and 80 mg. Hg doses of Neohydrin, the percentile increase was 323% after 80 mg. Hg as compared to 144% after 60 mg. Hg. It is of interest that the sodium excretion was greater in patients with heart failure than in the normal subjects. Although on doses of Neohydrin of 40 mg. Hg (4 tablets) there was no demonstrable effect on water excretion in the patients thus studied, this response was quite prominent with the 60 and 80 mg. doses (6 to 8 tablets). After a 60 mg. Hg dose the patients with cardiac disease showed a 32% (average) increase over the control levels, and after an 80 mg. Hg dose there was an increase of 99% (average) over the control values. After the administration of 1353Ex and 1431Ex to patients in heart failure, water excretion was increased from 20 to 50% with doses of 60 and 80 mg. Hg, with considerable variability among subjects.

There were no great differences among the diuretics in the amount of mercury excreted in the urine in 24 hours, which was roughly 5 to 10% of that ingested. The absolute amount excreted in the urine was greater with the larger doses and was

TABLE 5.—*Tissue Content of Mercury Seven Days After Ingestion of Neohydrin (Dose Containing 60 Mg. Hg)*

	Total Hg, Mg.		
Dog No.'	Heart	Liver	Kidneys
1	0.00	0.36	0.61
2	0.00	1.93	0.36
3	0.02	0.19	0.44
4	0.00	0.60	0.00
5	0.00	0.34	0.36
6	0.06	1.35	0.88
7	0.02	1.15	0.38
8	0.00	0.48	0.21
9	0.03	1.02	0.68
10	0.00	0.92	0.43
Mean	0.01	0.83	0.44

almost in direct proportion to the amount ingested. Urinary mercury excretion was greater after Neohydrin (chloro mercurial) than after the two thiol mercurials, 1431Ex and 1353Ex. This is probably a reflection of better absorption of the former, which may also account for the greater diuretic potency of Neohydrin. On continued daily administration, the amount of mercury excreted by the kidney was greater on the second day after starting therapy than on the first. However, on subsequent days the amount absorbed and excreted in the urine usually did not increase (Table 3).

Laboratory Observations.—It is evident that after a single dose of Neohydrin the maximal intestinal absorption and delivery of mercury to the kidney occurred during the first 24 hours. About one-third as much was excreted during the second 24-hour period. During the third and fourth 24-hour periods, negligible amounts were excreted. After 96 hours none could be detected in the urine. The decreasing amount of mercury in the urine is a reflection of the decreasing amount available for absorption in the intestinal tract. After 48 hours practically the entire amount of diuretic that was ingested had passed on through the intestinal tract and was excreted in the feces. On a regimen of continued daily ingestion one could expect a greater amount of mercury being delivered to the kidney during the second and

third day of drug administration than during the first because of the overlap due to the lag in fecal excretion (Table 4). This is also well demonstrated in Table 3 and is reflected in the lag in maximum diuresis produced by these orally administered diuretics. Sodium and water excretion frequently reached a maximum during the second and third day of drug administration to patients in heart failure. After four or five days the diuretic effect progressively decreased as the patient approached "dry" weight. In the dog studies, the only tissues showing residual mercury after the dogs were killed were the heart, liver, and kidneys. The amounts of mercury found in these tissues are presented in Table 5.

COMMENT

The data herewith presented indicate that the orally administered diuretic Neohydrin produces an increase in sodium and water excretion both in normal persons and in patients with heart failure. The patients in heart failure appear to be more responsive than normal subjects. Although the normal subjects did not appear to respond to doses containing less than 60 mg. Hg per 24 hours, it may well be that some patients in heart failure may obtain therapeutic benefit from smaller doses, since there was a definite increase in sodium excretion on a dose of 40 mg. Hg (4 tablets) per day. This may, over a prolonged period of daily drug administration, produce sodium depletion and therefore an edema-free state in patients with cardiac disease. The current observations support those of a previous study, in which it was found that with oral doses of Neohydrin containing less than 40 mg. Hg the therapeutic value as a diuretic was only a little better than placebo therapy, whereas with doses in excess of 60 mg. Hg the diuretic response was quite satisfactory and nearly as effective as semiweekly administration of meralluride by the parenteral route. It is unlikely that doses of less than this amount will maintain effective diuresis in patients with moderate to severe heart failure. It is also apparent that the chloro mercurial (Neohydrin) is superior to the thiol mercurials (1353Ex and 1431Ex) when administered orally. This may be a reflection of greater absorption from the intestinal tract in the case of Neohydrin. The percent of the mercury ingested which was excreted in the urine would support this supposition (Tables 1, 2, and 3). The relationship between water and electrolyte excretion is presented graphically in Charts 1, 2, and 3. There is a consistently greater percentile increase in sodium excretion than in water excretion. This is similar to the response after parenteral administration.[4]

The failure of any of the experimental diuretics to increase potassium excretion consistently, despite a rather marked diuresis in the case of Neohydrin, is of interest. This is in direct contrast to the effect on potassium excretion after parenteral administration of the same drugs.[4] Following the parenteral administration, the water diuresis and increased sodium excretion are paralleled by an almost equivalent increase in potassium excretion.

One of the major problems in the therapeutic use of mercurial diuretics is the necessity of using the parenteral route of administration. This is cumbersome and requires frequent visits to the doctor's office in many instances. The current studies indicate that it is feasible to administer Neohydrin by the oral route, since it is

4. Moyer, J. H.; Handley, C. A., and Seibert, R. A.: Clinical Diuretic Studies on Three New Mercurial Compounds, Am. Heart J. **44**:281, 1952.

absorbed from the intestinal tract and is delivered to, concentrated in, and excreted by the kidneys and liver in greater amounts than by any other body tissues. After systemic absorption most of the mercury is excreted in the kidney, where it inhibits reabsorption of sodium and water by the renal tubules. The amount of diuretic (estimated by Hg excretion) delivered to the renal tubules is adequate to inhibit this reabsorption of sodium and water, provided that the ingested dose is adequate

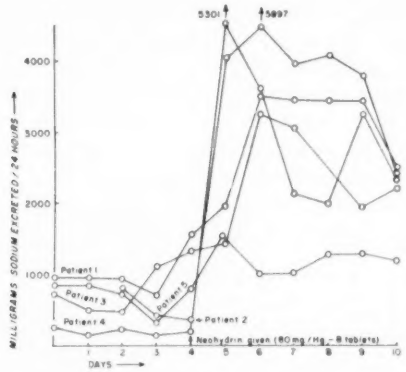

Chart 1.—Urinary sodium excretion expressed in milligrams per 24 hours in five patients (alternate cases studied) with heart failure. After three to four consecutive 24-hour control periods, Neohydrin was given orally in amounts containing 80 mg. Hg per 24 hours. Following administration of the drug there was a sharp increase in sodium excretion, which in some patients reached a maximum during the first 24 hours but in others was not attained until the second 24-hour period.

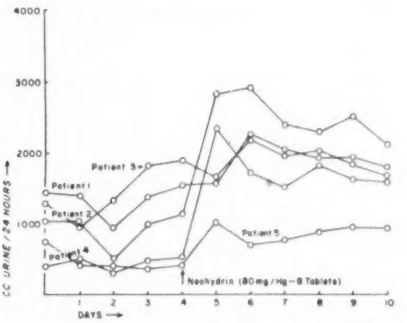

Chart 2.—There was a sharp increase in water excretion following Neohydrin (80 mg. Hg) administration (same cases as in Chart 1). Maximum diuresis was observed during the first 24 to 48 hours following the administration (oral) of Neohydrin.

and well tolerated. This amount of Neohydrin for normal persons appears to be that dose which contains about 60 mg. Hg, and it may be somewhat less (40 mg. Hg) for patients with heart failure. When the amount of Neohydrin containing 60 to 80 mg. Hg (6 to 8 tablets) is ingested, about 5 to 8 mg. Hg is delivered to the renal tubules over a 24-hour period, as estimated by the amount of mercury excreted. By far the greatest part of the ingested diuretic is lost in the feces. If the diuretic ingested orally is not absorbed in adequate amounts to deliver a diuretic

threshold dose of mercury to the renal tubules, then the diuretic becomes nothing more than placebo medication. In the case of meralluride administered parenterally the diuretic threshold dose appears to be 20 mg. Hg,[5] of which 90% is excreted by the kidney. If Neohydrin is the diuretic used, only one-fourth to one-half (5 to 10 mg.) of this amount of mercury would have to be delivered to the renal tubules, since Neohydrin has three to four times the diuretic potency of meralluride.[8] A dose of Neohydrin containing 60 to 80 mg. Hg (6 to 8 tablets) will do this. The increased mercury excretion in the urine after two or three days of daily drug administration suggests that this method can be expected to be more effective than a single daily intermittent dosage schedule, as, for example, giving the tablets twice a week. In the clinical studies of this drug[6] patients in heart failure were as well controlled on 6 to 8 tablets of Neohydrin by mouth as they were when receiving meralluride parenterally twice a week, which is in essential agreement with the observations of Goldman and Steigmann.[7] However, on doses of 4 tablets or less per day progressive cardiac failure developed in many of the patients. The heart failure in about 50% of the patients who did not experience an increase in the sever-

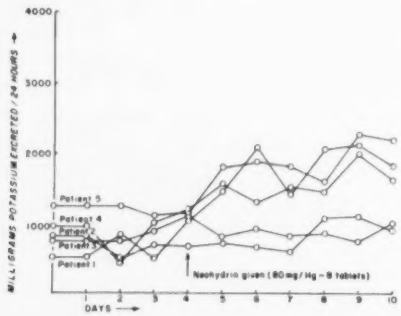

Chart 3.—Potassium excretion following orally administered Neohydrin. In contrast to parenteral administration of the diuretic, the effect on potassium excretion is inconstant. A slight increase in excretion was observed in some patients.

ity of the failure on this low dosage schedule after a period of three months was also controlled with placebos. Gastrointestinal disturbances were occasionally seen while these larger effective doses (6 to 8 tablets) were taken, but serious toxic manifestations were not encountered. Freedom from systemic manifestations has also been observed in dogs[8] which were given the drug parenterally three times per week for one year and then were killed. No evidence of visceral tissue damage was observed.

5. Clarke, D. A.; Modell, W.; Greiner, T.; Kwit, N. T.; Glück, J. L., and Gold, H.: The Dosage Response Curve for Comparison of Mercurial Diuretics, Am. J. M. Sc. **220**:156, 1950.

6. (*a*) Moyer, J. H.; Handley, C. A., and Wilford, I.: Results Over a Two-Year Period on Three Experimental Diuretics Administered Orally to Patients with Cardiac Failure, Am. Heart J. **44**:608, 1952. (*b*) Snyder, H. B.; Moyer, J. H., and Handley, C. A.: Clinical Results in the Treatment of Heart Failure and Observations on Water, Electrolyte and Mercury Excretion, M. Rec. & Ann., to be published.

7. Goldman, B. R., and Steigmann, F.: Experiences with a New Oral Mercurial, Proc. Central Soc. Clin. Res. **25**:34, 1952.

8. Handley, C. A.; Moyer, J. H., and Thomas, J. R.: The Effects from Prolonged Administration of Three Mercurial Derivatives of 2-Methoxy-Propylurea in Dogs, Proc. Soc. Exper. Biol. & Med., to be published.

In a previous study, in which the three experimental diuretics (1431Ex, 1353Ex, and Neohydrin) were administered parenterally, similar observations were made in respect to the relative diuretic efficacy.[4] The increase in sodium and water excretion showed greater statistical significance after Neohydrin than after the other two diuretics. The minimal dose of parenteral Neohydrin that was effective appeared to be that amount containing at least 10 mg. Hg. After parenteral administration 80 to 90% of the mercury in the diuretic is excreted in the urine.[6b] This again agrees with the current observation that at least 5 to 8 mg. Hg must be delivered to the renal tubules before the diuretic is dependable in the clinical management of heart failure. Generally speaking, it appears that 6 to 8 tablets of Neohydrin administered orally are about equivalent to 0.5 to 1 cc. of meralluride administered parenterally.

SUMMARY AND CONCLUSIONS

Electrolyte, water, and mercury excretion studies have been done after the oral administration of two thiol mercurial and one chloro mercurial (Neohydrin) experimental diuretics. The chloro mercurial, Neohydrin, appears to be the most effective diuretic, as estimated by the increased excretion of sodium and water. The increased effectiveness is probably due to greater absorption from the intestinal tract and consequently greater excretion in the urine. In addition, Neohydrin has more potent diuretic properties. The latter observation has been made following the parenteral administration of the three drugs to similar groups of patients in heart failure.

Approximately 5 to 10% of the amount of diuretic ingested is absorbed and excreted in the urine, as estimated by mercury excretion determinations. The renal threshold for the production of diuresis appears to be 5 to 8 mg. Hg. Therefore, the diuretic must be ingested in amounts containing 60 to 80 mg. Hg if adequate amounts are to be absorbed and consistently delivered to the renal tubules. Increased sodium excretion has been observed on smaller amounts (40 mg. Hg, 4 tablets), which was not associated with increased water excretion. This phenomenon may deplete stored sodium if the drug is given daily and thus prevent cardiac failure for prolonged periods of time despite the fact that acute diuresis cannot be demonstrated after this dose of Neohydrin.

DIFFUSE AND SOMETIMES RECURRENT COURSE OF DIFFUSE ARTERITIS

Observations and Report of a Patient Observed for Twenty-One Years

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THINKING relative to the so-called "collagen diseases" has been in the main in terms of entities or syndromes. The instances are not uncommon, however, in which the clinical picture begins as one syndrome, only to alter its course within months or years, to assume the picture of another. If the basic pathologic picture is kept in mind these transitional or intermediary manifestations are not disturbing. Furthermore, it is becoming more evident that medical thinking must include not only progressive vascular disease but also a disease of remissions and relapses. This is not a new concept but needs reemphasis. Osler [1] in his three papers on the visceral manifestations in "erythema exudativum multiforme," published between 1895 and 1903, in which he included 29 case reports, described patients whose conditions unquestionably would fall today into the categories of periarteritis nodosa and disseminated lupus. That Osler was aware of the possibility of remissions and relapses is shown by his remark in 1895 that "recurrence is a special feature of the disease and attacks may come on month after month or even through a long period of years." This observation has been generally neglected though it has been recognized in a speculative way by other authors. Thus Klotz [2] in 1917, though accepting a mortality rate of 100% in periarteritis nodosa, pointed out that patients with mild cases might recover, cases unrecognized because of the difficulties in a diagnosis dependent upon vascular lesions in internal organs. Arkin [3] in 1930, in a discussion of the pathologic variations in periarteritis nodosa, described a patient who had an acute illness followed by a four-year period of good health. Death occurred as the result of myocardial and renal failure. At autopsy there was evi-

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1. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme, Am. J. M. Sc. **110**:629 (Dec.) 1895; The Visceral Lesions of the Erythema Group, Brit. J. Dermat. **12**:227 (July) 1900; On the Visceral Manifestations of the Erythema Group of Skin Diseases, Tr. A. Am. Physicians **18**:599, 1903.

2. Klotz, O.: Periarteritis Nodosa, J. M. Res. **37**:1 (Sept.) 1917.

3. Arkin, A.: A Clinical and Pathological Study of Periarteritis Nodosa, Am. J. Path. **6**:401 (July) 1930.

dence of previous widespread arterial disease of the periarteritis nodosa type, with complete healing. In 1941, Blaisdell and Porter [4] reported a patient who died during the fourth hospitalization in a three-and-one-half-year period. All had been for acute episodes of illness. At autopsy the healed lesions of periarteritis were found. Death was due to renal failure.

In the past decade, with increased interest in diseases having diffuse arteritis, more and more diagnoses have been established ante mortem. As an accompaniment of this interest cases exhibiting remissions or healing have been recognized with greater frequency. It is being shown by biopsy, as has been noted in the past at autopsy, that fibrosis may occur in the lesions of periarteritis nodosa even though the process may be active elsewhere. In some instances, though healing may have occurred the vascular scarring may inevitably lead to death if vital structures such as kidneys and heart have borne the brunt of the arterial disease.

Goodman [5] published the case report in 1948 of a 17-year-old boy who, at the time of a stormy acute illness, was shown by biopsy to have acute arteritis. Two years later he was still well. King [6] described a patient having the lesion of periarteritis nodosa in the gallbladder, in whom symptoms had been present for two or three years. She was continuing to show clinical manifestations at the time of his report in 1948. Klein [7] reported a patient having had two bouts of an acute process, with proved arterial disease found by biopsy on each occasion, separated by 12 years of good health. The patient was well one year after the second attack, at the time of the report. Klein's second case is that of a girl shown to have a vascular lesion in the appendix 11 years before. She had been well during this period of time. From this it may be assumed that healing of vascular lesions may take place, with recovery for the moment, to be followed by exacerbations at other sites and times. If this is true, it is probable that in some patients healing may be permanent, without recurrence.

We wish to illustrate the variability of arteritis as a disease by the use of the clinicopathologic pictures of three cases. The first two illustrate occasionally encountered examples of diffuse arteritis and are acceptably diagnosed as periarteritis nodosa.

REPORT OF CASES

CASE 1 (205296).—M. M., an 8-year-old girl, was admitted to the pediatric ward of Vanderbilt University Hospital on Nov. 13 and died on Nov. 27, 1951.

The child had been well during infancy and early childhood except for frequent upper respiratory infections accompanied by sore throat. There was no history of rheumatism.

Present Illness.—Two weeks before admission an upper respiratory infection with fever and sore throat developed. Several days later there was headache and pain appeared in the back and periumbilical area. Then anuria developed. Eight days before admission the patient was admitted to the hospital in her home town because of generalized edema and pharyngitis. Nausea and vomiting occurred (she was given 300,000 units of penicillin). The urine at that time showed

4. Blaisdell, E. R., and Porter, J. E.: Healed Stage of Periarteritis Nodosa, New England J. Med. **227**:1087 (June 24) 1941.

5. Goodman, M. J.: Periarteritis Nodosa with Recovery: Report of an Unusual Case Apparently due to Sensitivity to Sulfadazine, Ann. Int. Med. **28**:181 (Jan.) 1948.

6. King, F. H.: Protracted Course in Periarteritis Nodosa, J. Mt. Sinai Hosp. **15**:97 (July-Aug.) 1948.

7. Klein, S. P.: Periarteritis Nodosa: Study of Chemistry and Recovery, with Report of 2 Cases, Arch. Int. Med. **84**:983 (Dec.) 1949.

casts, a few white blood cells, a specific gravity of 1.020, a 4+ albuminuria and a nonprotein nitrogen level of 138 mg. per 100 cc. The blood pressure ranged from 116/85 to 136/100, with a pulse rate varying from 80 to 130.

Physical Examination.—At the time of the patient's admission to Vanderbilt University Hospital the temperature was 98.6 F., pulse rate 120, and blood pressure, 120/95. The patient was semistuporous, acutely and severely ill. A "flea-bite" type of rash was noted over the extremities. The malar eminences were flushed. There was generalized non-pitting edema. No remarkable adenopathy was present.

There was a hemorrhage in the left conjunctiva; slight papilledema was present. The tonsils were mildly hyperemic. The lungs had a few crepitant rales at the bases. Examination of the heart revealed no abnormalities. The abdomen showed generalized tenderness with some guarding, especially in both lower quadrants and in the left costovertebral angle.

The clinical impression was that the patient had acute glomerulonephritis with uremia.

Laboratory Studies.—On admission the urine showed albuminuria of a 2+ degree, and microscopically innumerable red cells and many white cells were seen. The blood findings were hemoglobin 9.5 gm., red cell count of 4,950,000, leucocytes 24,600, packed cell volume of 29%, and a differential picture of 87% polymorphonuclear cells, 11.5% lymphocytes, and 1.5% monocytes, with a total eosinophile count of 74. Sedimentation rate was 29 mm. Blood chemical determinations were nonprotein nitrogen 216 mg. per 100 cc., chlorides 71.1 mEq. per liter, calcium 7.5 mg., phosphorus 23.5 mg., cholesterol 160 mg., total serum proteins 5.36 gm., albumin 3.3 gm., and globulin 2.06 gm. per 100 cc. The blood Kahn test and a battery of agglutination tests were negative. Blood culture was negative for pathogens; urine culture revealed paracolon organisms on several occasions.

Clinical Course.—During the first 10 days recurrent massive epistaxes and persistent vomiting of "coffee-ground" material were troublesome. A systolic murmur and pericardial friction rub developed. Four transfusions were given. A specimen of muscle was taken for biopsy.

On November 26 the patient complained bitterly of upper abdominal pain. Her condition rapidly became worse; she was somewhat cyanotic and shallow respiration developed. Friction rubs were heard over the right chest. The blood pressure was 140/100. During the next 24 hours, before death, cyanosis and dyspnea increased; an irregular cardiac rhythm appeared. The patient became comatose and died.

During the hospital stay intermittent fever was present, the temperature ranging from 100 to 102 F. The blood pressure varied from 130/80 to 170/110.

A dozen urinalyses showed a persistent 2+ or 3+ albuminuria, innumerable red cells, many white cells, and occasional hyaline casts, the highest specific gravity being 1.022. Blood nonprotein nitrogen levels varied from 188 to 224 mg. per 100 cc., chlorides from 69.3 to 91.8 mEq. per liter, CO_2 from 21.3 to 25 mEq. per liter, serum calcium from 5.1 to 7.5 mg. per 100 cc., and phosphorus from 16.5 to 24 mg. per 100 cc. Serum protein levels remained essentially unchanged. Hemoglobin levels varied from 5.5 to 10 gm. dependent upon transfusions. A leucocytosis was almost constantly present, with cell counts of 10,000 to 24,600. The differential cell count picture remained unchanged.

Chest films revealed some cardiac enlargement and small amounts of pleural fluid.

Eight electrocardiograms varied from showing no abnormalities on several occasions to some showing mild T-wave changes.

Autopsy.—Gross Examination: The external findings included slight obesity and a tendency towards puffiness of the skin. A macular rash was present over the forearms, but no other skin lesions were found. There were small, barely palpable axillary and inguinal lymph nodes.

The peritoneal cavity contained 500 cc. of clear straw-colored fluid, and the serosa was shiny and thin throughout. Slight retroperitoneal edema was evident. The mesenteric nodes were slightly enlarged and purple in color due to congestion. The right pleural cavity contained 400 cc. of clear fluid, and the left contained 100 cc. of similar fluid. The pleural surfaces were smooth and free of lesions. Several mediastinal nodes were enlarged to a moderate degree and contained caseous material on section.

The pericardial cavity was tremendously distended, containing 1,000 cc. of very bloody fluid. A thick shaggy layer of fibrin covered both visceral and parietal layers of pericardium.

Heart. The left side of the heart was moderately enlarged, and the myocardium appeared coarse. The endocardium throughout was thin and translucent, with no mural thrombi or vegetations. The valves were thin, with slight fibrous thickening along the free edge of the mitral valve. Subendocardial hemorrhage was noted in the right atrium and left ventricle. The aorta and other great vessels were normal.

Lungs. The right lung weighed 175 gm., and the left 140 gm., and both appeared completely collapsed. Several small subpleural tubercles were present in the right lung, the largest being 5 mm. in diameter. These nodules were calcified without exception. In the left lung there was a walled-off area of caseation 1 cm. in diameter. Generally, the lungs appeared atelectatic. No antemortem clots were found in the pulmonary vessels, and the bronchi contained only moderate amounts of mucus.

Gastrointestinal tract. The examination of the gastrointestinal tract revealed no abnormalities save superficial erosion of the lower esophagus.

Liver. The liver weighed 1,360 gm. and was moderately enlarged with rounding of the edges; it appeared fatty. There were several tubercles beneath the capsule, and numerous irregular depressed purple areas up to 2 cm. in diameter were noted. The gallbladder was thin-walled and normal.

Spleen. The spleen was slightly enlarged, weighing 140 gm., and the capsule was somewhat thick. Several tubercles were seen, but there were no other focal lesions. An accessory spleen, 1 cm. in size, was found embedded in the tail of the pancreas.

Pancreas. The pancreas was firm in consistency, with the lobules fixed. It was free of focal lesions.

Adrenal glands. The adrenal glands were normal in size and configuration, with a few small nodular areas of cortical hyperplasia.

Kidneys. Both kidneys were moderately enlarged, the right weighing 180 gm., and the left 190 gm. They were identical in appearance. The capsule was thin and stripped easily, and the cortical surface was smooth, with myriads of petechial hemorrhages. On section the cortex was of normal thickness and its striations somewhat indistinct, with more petechial hemorrhages visible on the cut section. The pyramids were well defined and congested. The pelvic mucosa was thick, granular, and opaque, with induration of the surrounding connective tissue. The upper half of each ureter was similarly involved with thickening and induration of the wall and granularity of the mucosa. The bladder was free of lesions and the internal genitalia were not remarkable.

Neck organs. On examination of the organs of the neck two parathyroid glands were identified, one 3 mm. and another 11 mm. in the broadest diameter. The thyroid was normal.

Central nervous system. Examination of the central nervous system was not done.

Microscopic Examination: Heart. An organizing fibrinous exudate was present on the epicardial surface, with a paucity of polymorphonuclear cells. The myocardial fibers appeared to be slightly larger than normal, and careful search revealed no Aschoff bodies. However, there was cellular exudate composed of large mononuclear cells and some segmented cells about some small arteries. There was edema of the walls of involved vessels, with no necrosis.

Lungs. In most areas the alveoli were collapsed. Several foci of caseous necrosis were included in the sections; there was a surrounding granulomatous reaction. The pulmonary vessels were not abnormal, and the bronchi exhibited the usual structure.

Gastrointestinal tract. There was superficial ulceration of the esophagus, with a considerable amount of cellular exudate, in which the polymorphonuclear cells predominated. Other than this lesion, the only striking changes in the gastrointestinal tract were in the small arteries. The submucosal arteries in sections of the stomach, small bowel, and large bowel exhibited segmental necrosis of their whole walls, with the usual elements replaced by a bright pink, hyaline material in which there were innumerable nuclear fragments. There was an associated cellular exudate of polymorphonuclear cells and large mononuclear cells. It was noted with interest that eosinophiles were not found in association with these or other vascular lesions and no appreciable thrombosis was found within the lumens of affected vessels. Earlier lesions, consisting of edema of the vessel wall and small foci of necrosis, were seen on occasions without an associated cellular exudate. (The vascular lesions are described here in some detail, as they are representative of those seen in other organs.)

Liver. The parenchymal structure was not appreciably altered. Scattered arteries in the triads exhibited necrosis and cellular exudate of the type described above. A section of gallbladder wall showed similarly involved small arteries.

Pancreas. Occasional small groups of round cells were seen in the interstitial tissue. A necrotic artery was found here and there in the interlobular connective tissue. Some small ducts contained hyaline casts.

Spleen. The splenic sinuses were engorged, but the over-all architecture was preserved. No necrotic arteries were observed; many of the penicillary arteries had hyaline, moderately thickened walls.

Adrenal glands. There were no lesions in the adrenal glands. In the periadrenal connective tissue there were numerous necrotic arteries of the type described previously.

Kidneys. Surprisingly, the glomeruli had a relatively normal appearance. Many tubules were filled with red cells, hyaline casts, and eosinophilic debris. The arterioles were normal in appearance, while necrotic interlobular arteries were very frequently encountered; necrotic segments of arcuate arteries were also seen occasionally. Many arteries in the peripelvic connective tissue were smudgy and completely necrotic, with heavy exudation of inflammatory cells. The pelvic mucosa was thickened by this inflammatory exudate. Necrotic arteries were prominent in sections of the upper ureter (Fig. 1*A*). Arterial involvement was marked in the perivesical connective tissue, and an acute cystitis was present. The sections from the internal genitalia showed nothing remarkable.

Lymph nodes. Caseous necrosis was present in a section of mediastinal lymph node. Other nodes exhibited very marked edema and phagocytic cells, often with ingested red cells, and polymorphonuclear cells were abundant in the sinusoids.

Bone marrow. All the usual elements were present in the bone marrow in normal proportions. No lesions were found.

Striated muscle. Sections of diaphragm and other striated muscles revealed no arterial change or myositis.

Thyroid and parathyroid glands. The sections of these structures were not remarkable; the parathyroid gland examined was about twice the normal size.

Bacteriology. Smears of the caseous material in the mediastinal nodes contained numerous typical acid-fast organisms. Cultures of the bloody material in the pericardial sac showed no growth, and a guinea pig inoculated with this material was found to be healthy and free of lesions after seven weeks.

Comment.—This case offers an example of the fulminant clinical course which may occur in disseminated arteritis following an acute upper respiratory infection. The clinical manifestations were in the main of renal origin, and the patient undoubtedly died in renal failure.

The immediate cause of death, as determined at autopsy, was the large hemopericardium, probably resulting from uremia in conjunction with the necrotizing arteritis demonstrable microscopically. The severe acute involvement of small arteries in many organ systems was quite striking. The vascular lesions seemed to be of uniform age and type, as though all the profound changes in the vascular bed represented a widespread response to injury.

CASE 2 (194747).—J. G., a 9-year-old boy, was admitted to the pediatric ward on Nov. 30, 1950, and died on Jan. 14, 1951. He was referred to the Vanderbilt University Hospital with a diagnosis of acute nephritis.

Infancy and childhood were free of disease except for measles and frequent bouts of tonsillitis. He had been immunized against smallpox, diphtheria, typhoid, and pertussis. Allergic diseases had not been manifest.

Present Illness.—Five weeks before admission tonsillitis developed and the patient was treated with four injections of penicillin. One week later he returned to school, and at about this time nausea and "stomach ache" developed while he was at school. That night there was considerable malaise and some lethargy. On the following morning the family physician, finding edema, made a diagnosis of nephritis. Complete bed rest was enforced at home for five days without improve-

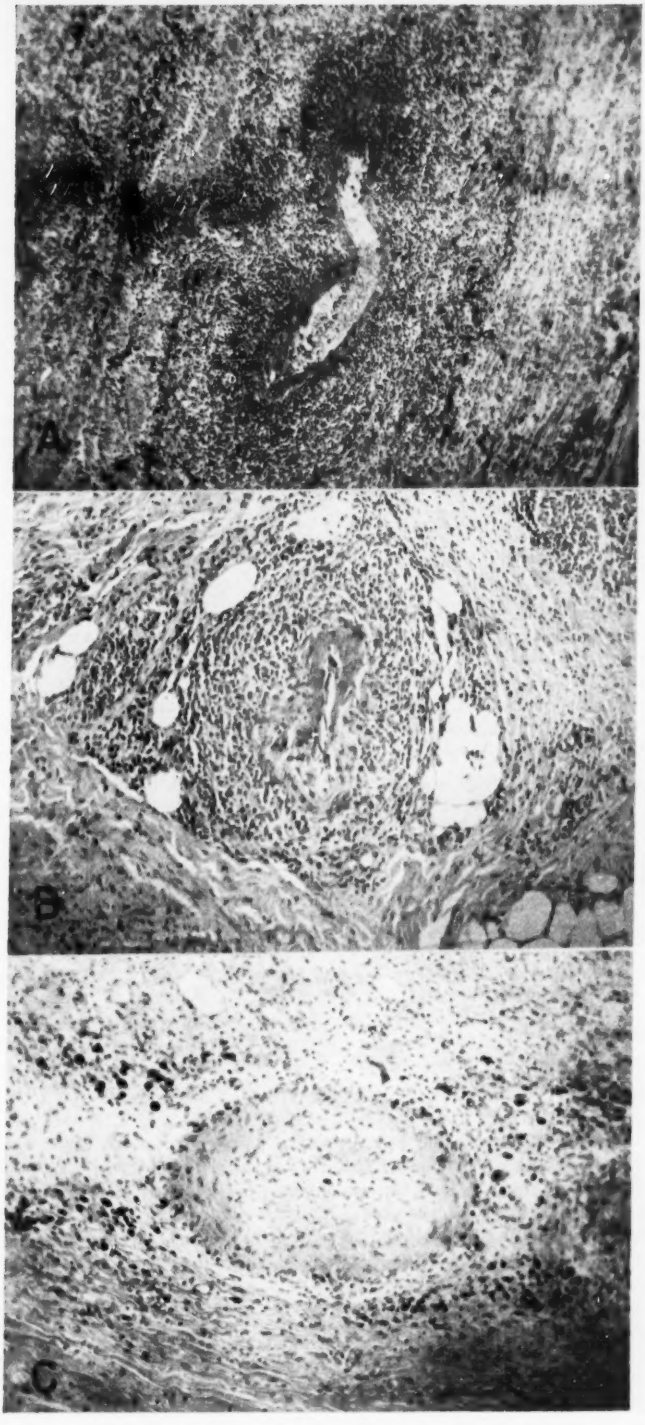

Fig. 1.—*A* (Case 1), a section of ureteral wall. Two foci of necrosis of the vessel wall are separated by a segment of normal artery. Polymorphonuclear leucocytes predominate in the exudate. *B* (Case 2), appendiceal artery five weeks before death. On one side some normal medial cells persist, while the remainder of the vessel wall is necrotic. The leucocytic exudation is very heavy. *C* (Case 2), artery in gallbladder wall at autopsy. Fibroblastic proliferation and recanalization are evident. Hemosiderin-containing macrophages are numerous; few other inflammatory cells persist.

ment, and therefore the patient was admitted to the hospital in his home town (this was three and one-half weeks before admission to Vanderbilt University Hospital). Several days later hematuria and albuminuria developed. Marked nausea occurred at this time with vomiting. While the patient was in the hospital treatment consisted of antibiotics—penicillin, streptomycin, chloramphenicol (Chloromycetin), and chlortetracycline (Aureomycin). Five transfusions, 250 cc. each, of fresh blood from the father were given, the last one two days before admission to Vanderbilt University Hospital.

On the day before admission a macular, erythematous rash had developed over the face, chest and arms, thought to be due to transfusions, and diphenhydramine (Benadryl) had been given. In the week before admission there had been epistaxes, one large one estimated at a half cupful (0.12 liter) of blood. During the week before admission the urine was deep red in color.

The referring physician reported hemoglobin 8.5 gm., urea nitrogen 150 mg. per 100 cc., creatinine 6 mg. per 100 cc., and 2+ albuminuria, with microscopic findings in the urine of red cells and 6 to 8 white cells per high power field. An electrocardiogram was said to be normal.

Physical Examination.—On admission the temperature was 101.4 F., pulse rate 130, and blood pressure 175/100. The boy appeared to be acutely ill and distressed, complaining of pain in the arms and legs, and presented a slightly cloudy sensorium. The skin showed a macular erythematous rash on the face, arms, trunk, and particularly on the chest, which did not blanch on pressure and which varied in intensity. There was pallor; deep red circles were present beneath the eyes. There was only moderate edema of the ankles.

There was no lymphadenopathy. The pupils were normal; the retinas showed moderate papilledema but no spasm of arterioles, nor hemorrhage, nor exudate. The mucous membranes were slightly pale, the tonsils small. The lungs were clear. The heart was not enlarged; the sounds were of fair quality; a Grade I systolic murmur was heard at the apex and along the lower left sternal border. The pulmonic second sound was greater than the aortic second sound.

A moderate amount of ascites led to diffuse distension of the abdomen; it was tender on palpation. The liver was palpable 2 cm. below the costal margin, the edge being sharp and tender; the spleen was not palpable. There was some tenderness in the costovertebral angle. The genitalia were normal. The extremities demonstrated fair muscle tone; the deep reflexes were hypoactive in the lower extremities. The cranial nerves were intact.

Laboratory Studies.—On admission the urine showed albuminuria of 1+, with rare granular and hyaline casts and 10 to 35 red cells and 4 to 20 white cells per high-power field. The blood revealed hemoglobin 8 gm., red cell count of 3,170,000, leucocyte count of 31,500, and a differential picture of 86.5% polymorphonuclear cells, 0.5% eosinophiles, 11.5% lymphocytes, and 2% monocytes. Total eosinophile count was 137. Sedimentation rate was 25 mm. Blood chemical determinations were nonprotein nitrogen 148 mg. per 100 cc., chlorides 87.5 mEq. per liter, and calcium 8.5 mg., inorganic phosphorus 9.6 mg., cholesterol 89 mg., total serum proteins 7.15 gm., albumin 3.46 gm., and globulin 3.69 gm. per 100 cc. The blood Kahn test was negative. Lumbar tap revealed a pressure of 200 mm.; the spinal fluid showed 3 cells per cubic millimeter, protein 21 mg. and sugar 96 mg. per 100 cc., and a negative Wassermann reaction. Examination of stool was positive for blood.

Clinical Course.—Nonfermenting organisms were cultured from the urine. Treatment was begun with digitalis and magnesium sulfate. In the first several days lethargy increased and edema and ascites persisted; a loud systolic murmur and a pericardial friction rub developed.

Since the hemoglobin and red cell count had dropped to 5.5 gm. and 2,320,000, respectively, a transfusion was given on Dec. 3. This resulted in clinical improvement and a rise in hemoglobin to 13.5 gm. The organism cultured from the urine had been shown to be sensitive to chloramphenicol, and therefore treatment with this antibiotic was begun. By Dec. 7 the patient was again lethargic; the temperature had been up to 101 F. for the preceding 24 hours. Blood pressure was 160/90.

On Dec. 9 pain and tenderness in the lower right quadrant and a temperature of 101 F. developed. An appendectomy was performed on the following day. The appendix was normal grossly, but the entire small bowel was edematous; the mesenteric nodes were enlarged. The left kidney was unusually fixed and hard (cultures from mesenteric nodes were negative for pathogens).

Pathologic Report.—Sections of the appendix revealed no inflammation of the mucosa. Almost every small artery exhibited eosinophilic necrosis of its wall, nuclear fragmentation, and a surrounding cellular exudate with polymorphonuclear leucocytes predominating (Fig. 1*B*).

On Dec. 14, because of the pathologic finding of necrotizing arteritis in the sections of the appendix, cortisone therapy was begun (225 mg. on the first day, 150 mg. on the second, and 75 mg. daily thereafter). Severe epistaxis occurred, and by Dec. 16 the hemoglobin had again dropped to 6.2 gm.; 500 cc. of blood was given. This was reepated two days later.

Cortisone therapy was continued for eight days, with rising temperatures after the first two days. The patient was discharged to his home for Christmas, returning 60 hours later. Within a few hours of his returning home severe epistaxis developed, requiring nasal packs and a 500 cc. transfusion of blood by the family physician. On the patient's return to the Vanderbilt University Hospital the findings were the same as upon discharge.

Two days later the blood pressure rose to 200/150. Epistaxis continued. Four transfusions were given between Dec. 26 and 30; cortisone therapy was discontinued on this day because of progressive disease and rising temperature. The blood pressure remained at a 200 mm. systolic level, the diastolic level varying from 100 to 150 mm.

From Jan. 2 to 14, the day of death, muscular twitchings, with occasional generalized convulsions, were present. Tachycardia, hypertension, and fever (temperature 103 F.) persisted.

During the hospital stay many laboratory studies were done. These will not be detailed but will be summarized only. More than 20 urinalyses always showed a 1 to 2+ albuminuria, with hyaline and granular casts and white and red cells, the maximum specific gravity being 1.015. Blood nonprotein nitrogen levels varied between 106 and 164 mg. per 100 cc. Chloride levels were from 83.2 to 92.4 mEq. per liter. Hypocalcemia and hyperphosphatemia persisted. Hemoglobin levels fluctuated from 5.15 to 13 gm., dependent upon transfusions. Leucocytosis was constant, with a cell count from 17,000 to 34,800. The differential picture was noted on admission and remained essentially unchanged. Total eosinophile counts varied from 28 to 161 per cubic millimeter during the first week; thereafter none were found.

Roentgenographic studies of heart, lungs, and abdomen were not remarkable.

Five electrocardiograms were abnormal, varying from time to time, but consisted of ST-segment and T-wave changes.

Blood cultures were negative for pathogens; throat cultures showed only normal flora. Cultures of the urine revealed coliform organisms and staphylococci.

Autopsy.—Gross Examination: External examination of the body revealed evidence of rather poor nutrition and a petechial skin rash confined to the regions of the ankles. The superficial lymph nodes were not enlarged. The appendectomy incision was well healed.

There was no free fluid in the peritoneal cavity, and the only adhesion was a fibrous one between the omentum and anterior abdominal wall. The peritoneum was thin and shiny throughout; petechial hemorrhages were noted in the upper peritoneal reflections. The abdominal lymph nodes were purple in color but not significantly enlarged.

No free fluid was present in the pleural cavities; a 3 mm. hemorrhagic nodule was present beneath the right parietal pleura. The pericardial cavity contained no excess fluid, and the surfaces were shiny and thin throughout.

Heart. The heart was enlarged and weighed 210 gm.; there was marked left ventricular hypertrophy. A 4 mm. hemorrhagic nodule was noted on the anterolateral surface of the left ventricle; grossly it did not appear related to a vessel. The myocardium was pale and firm, and several 2 mm. grayish nodules were seen to project above the surface of cut section of the left ventricle. There was subendocardial hemorrhage in the left ventricle. The valve leaflets were thin and unchanged save for three petechiae in the mitral leaflets. The aorta and great vessels presented no abnormalities.

Lungs. The lungs were well expanded; the right weighed 210 gm., and the left 180 gm. A few petechial hemorrhages were seen on the posterior aspect of the lower lobe of the left lung. Firm thrombi were found within some of the secondary branches of the pulmonary arteries to each lower lobe, partially occluding the vessels. The bronchi were normal.

Gastrointestinal tract. There was a superficial ulceration in the lower esophagus. It was believed that there was some thickening of the wall of the upper small intestine, but this was not marked. Petechial hemorrhages were seen in the mucosa of the lower jejunum and ileum. The appendiceal stump was well healed.

Liver. The liver was large with rounded edges; it weighed 1,730 gm. Three 4 mm. purple nodules were noted along the insertion of the falciform ligament. A yellow color was evident generally on the cut surface, with focal areas of a purple gray color. There were grossly visible thrombi within small vessels in these areas. The gallbladder wall was somewhat thick, but the mucosa was intact.

Pancreas. The pancreas was firm and normal in size and configuration, without focal lesions.

Spleen. The spleen weighed 140 gm., and had a thin capsule, and the Malpighian bodies were quite prominent.

Adrenal glands. The adrenal glands appeared somewhat small but presented a normal appearance on section.

Genitourinary tract. The two kidneys were similar, each weighing 190 gm. and having a thin capsule which stripped easily. The surface was smooth, with many petechial hemorrhages. The cortex was of the usual thickness, somewhat swollen, and irregular small hemorrhages were confined to this area. The medullae were normal, as were the pelves of the kidneys. The ureters were thin, and the bladder exhibited only occasional submucosal petechiae. The genitalia were not remarkable.

Brain. The brain weighed 1,130 gm., and on section, after formalin fixation, a very small area of encephalomalacia was found at the superior medial aspect of the parietal lobe. No other gross lesions were present.

Microscopic Examination: Heart. The myocardium was normal except for hypertrophy of the fibers. An epicardial artery was remarkably altered. Its lumen contained an organizing thrombus, and its wall was disorganized, with collagenous replacement of the usual medial elements. Numerous large phagocytic cells were seen about it; many of these contained hemosiderin particles. This lesion represented the epicardial nodule described grossly. No other vascular lesions were seen in arteries of the heart. The aorta was normal microscopically.

Lungs. Many bronchi were filled with polymorphonuclear leucocytes, with small surrounding areas of pneumonitis. One larger and one small pulmonary artery contained organizing thrombi within their lumens; otherwise the vessels were not remarkable.

Gastrointestinal tract. There was remarkably little change evident in sections of the gastrointestinal tract save for the alterations in the submucosal arteries. In some areas, especially in the large bowel, these vessels exhibited the fibrinoid appearance associated with a necrotizing arteritis. However, even in these acutely involved vessels, fibroblastic proliferation was evident, with fragmentation of the fibrinoid material. Various stages of healing were observed. Some of these small arteries showed no evidence of acute damage, inasmuch as the vessel wall had been converted into a collagenous type of tissue, with only a few large phagocytes containing hemosiderin as the remainder of the former cellular exudate. The lumens of these "healed" vessels were appreciably diminished.

Liver. There was considerable fat in the parenchymal cells; this was marked in the central areas. Occasional arteries exhibited scarring, with local accumulation of hemosiderin. A section of gallbladder wall showed several segments of a healing artery (Fig. 1*C*); recanalization was evident.

Pancreas. The pancreatic tissue appeared normal. No significant alteration of the vessels was found.

Spleen. The usual structure was evident, with no change in the vessels. Pigment-laden macrophages were fairly numerous.

Adrenal glands. Numerous arteries in the periadrenal connective tissue exhibited fibrosis, pigment deposition, and obliteration of their lumens. The adrenal glands had a normal appearance.

Kidneys. Increased cellularity and adhesions were seen in occasional glomeruli. The glomerular basement membrane appeared thickened. Many tubules appeared moderately dilated, and rare cortical tubules contained hyaline casts. Small arteries in some areas exhibited the proliferative reaction described above; none showed acute necrosis. The arterioles were not a tered.

Bladder. There was hemorrhage in the mucosa, and some small thick-walled mucosal arteries were seen.

Lymph nodes. The lymph nodes microscopically exhibited edema and fair numbers of phagocytic cells in the sinusoids.

Bone marrow. There was evidence of normal erythropoiesis.

Brain. One section showed evidence of old infarction as there were numerous lipid-laden macrophages and a proliferation of glial cells in a discrete area. No vascular lesions were found.

Comment.—Here again was an instance in which, following an acute upper respiratory infection, complicated by the administration of several antibiotics, the major manifestations were those of vascular disease of the kidneys ending in renal failure. However, during life the patient demonstrated arterial involvement of other organs. There were a systolic murmur, hepatomegaly, and involvement of other abdominal viscera leading to an appendectomy.

There was a diffuse necrotizing arteritis of the appendix five weeks before death. Microscopic examination of the autopsy material did not reveal any similarly acute arterial lesions. Instead, the changes were characteristic of healing and repair in innumerable small arteries, obviously at the site of previous destructive lesions. The various stages of repair were observed. Small areas of fibrinoid necrosis of arterial walls persisted in the wall of the large bowel. In other areas, especially in the gallbladder wall, healing had progressed to the point of early recanalization, with almost complete disappearance of the characteristic cellular exudate, except for macrophages containing hemosiderin. Although it is impossible to estimate the degree of recanalization which might have occurred eventually, it is reasonable to assume that sufficient reestablishment of vascular channels might have taken place to insure an adequate circulation.

CASE 3 (46723).—Mrs. P. P. was admitted to the Vanderbilt University Hospital in 1932, at the age of 25 years. Admission was to the surgical service because of pain in the right flank and right abdomen.

(The history will be presented by systems, organs, or symptoms to avoid confusion in following a clinical course of 20 years.)

Clinical Data.—Epistaxis, described as so massive that the patient almost "bled to death," occurred in 1916 and again in 1924. She recalls recurrent epistaxis as a child from age 9 years; it often occurred at play. A subsequent attack occurred in the spring of 1951. In December of that year recurrent epistaxis was troublesome for a month. A severe attack occurred in May, 1952.

Tonsillitis recurred frequently in her younger days until tonsillectomy in 1928.

In 1925 (at the age of 18 years) the patient suffered from some form of arthritis. The attack kept her in bed for six months. The attack began in the right thumb and extended to involve the whole hand, so that movement of any of the joints of the part became impossible. Tenderness and pain were described as severe. The right knee also became swollen and stiff, remaining so for one month. The fingers were so stiff that later they had to be manipulated, or "broken up," at the end of the six-month period. Fever and sweats were present throughout the period. (There was no vaginal discharge at the time, and the patient's first sexual exposure was three years later, after marriage. A gonococcal infection seems unlikely.) The right wrist remained permanently stiff with limited motion thereafter. An x-ray film taken years later showed obliteration of joint spaces between the carpal bones, suggesting the residuum of infectious arthritis.

In December 1950 the patient complained for the first time of pain and aching in joints, fingers, elbows, and shoulders. This complaint also appeared at the time of admission to the medical service in July 1951, the symptoms being referred to the knees, wrists, and ankles.

Cardiorespiratory Symptoms: Since childhood there had been dyspnea on exertion so that the patient recalls she could not match the activity of her playmates; not uncommonly she had to lie down at play to breathe. (She was thought to have the "phthisic.") This has been a prominent more or less constant symptom, as indicated in the hospital record of the past two decades.

Attacks of paroxysmal nocturnal dyspnea, awakening the patient from her sleep and forcing her to sit upright, began at age 9 or 10 years. Wheezing accompanied these attacks at first so she could be heard across the room. This characteristic was lost in the twenties, though the

attacks of nocturnal dyspnea have continued. This has also been a prominent recurrent manifestation since that date. For example, it was emphasized in her history in 1939, while she was on the obstetrical service, the attacks being described as lasting 15 to 20 minutes. Palpitation always accompanies the paroxysmal nocturnal dyspnea and orthopnea. At the time of admission to the medical service, in February 1948, the patient reiterated the recurrence of attacks of dyspnea at night with the accompanying palpitation. Dyspnea, exertional as well as paroxysmal, has persisted throughout the course of the disease to the present time.

Even in 1932 the patient described precordial pain related especially to work and other exertion.

Bilateral pain in the shoulders was complained of bitterly, in association with the pain in the right flank and abdomen which led to admission to the Surgery Clinic in 1947. Hypodermic injections for pain were necessary at times.

After admission to the medical service in February 1948 the patient was observed to have sudden attacks of pain in the right upper abdomen accompanied by "squeezing" pain radiating to the back and both shoulders.

Some seven weeks after admission (April 1, 1948) she suddenly complained of a sense "as if she were to die." During cardiac auscultation the rate increased to 160, the radial pulse was impalpable, and profuse perspiration occurred. Pressure on the carotid artery and later a finger down her throat caused a reversion to normal rhythm. This episode was presumed to represent an attack of paroxysmal tachycardia.

On April 13 the patient suddenly screamed with severe pain in both shoulders radiating down both arms and to the chest anteriorly and posteriorly. The blood pressure and pulse were unobtainable; the apical rate was 120 with sounds of fair quality. The patient was cold, pale, and clammy. Morphine intravenously was necessary for the relief of pain. An electrocardiogram soon thereafter showed no change. Dramatic and identical episodes occurred on April 16, 17, twice on April 28, and on May 24. Each time, pulse and blood pressure were unobtainable. The pain varied, at times beginning in the shoulders, again substernally, and in all but the first attack it radiated only to the left shoulder. Morphine always was needed for relief. On the days between these episodes there was almost constant precordial pain with radiation to the interscapular areas, the left chest, neck, and left arm and hand, with variations. Hypotension was recorded during this period of time. Seven electrocardiograms during these days showed varying ST-segment and T-wave changes; there was never a clear-cut pattern of infarction. The patient remained afebrile.

At the clinic visits in the latter half of 1948 and during 1949 recurrent attacks of precordial pain with radiation to neck, left arm, and fingers continued to appear. They were brought on by exercise or excitement; at times they were very severe.

While in the hospital on May 8, 1950, the patient had a severe attack of pain in the left chest, with radiation to the left arm. The blood pressure was 170/100, and an electrocardiogram was normal. Deep precordial pain with radiation to the left arm continued throughout 1950. Relief often was obtained by glyceryl trinitrate (nitroglycerine). These attacks often awakened the patient from her sleep. The electrocardiogram showed ventricular premature contractions on several occasions.

During the month of hospitalization beginning Dec. 4, 1950, the patient had recurrent bouts of precordial pain with radiation to the neck and left arm, at times relieved by glyceryl trinitrate, again requiring morphine. Palpitation and tachycardia accompanied the attacks of pain. A sound interpreted as a pericardial friction rub was heard for a time over the third left interspace. An apical blowing systolic murmur was described for the first time. Several electrocardiograms showed no abnormalities during this admission. In one attack of pain the blood pressure rose to 180/105.

Anginal attacks persisted throughout the spring of 1951. The usual pattern of radiation was present. Tachycardia of 100 to 120 beats per minute was common during visits to the clinic. At times an apical systolic murmur was described; again it apparently was absent. Electrocardiograms were normal.

Severe recurrent precordial pain with radiation to the left neck, shoulder, and arm was the reason for readmission to the hospital on July 24, 1951. There had been particularly severe "crushing" pain referred to the left shoulder for the 18 hours before admission. Several electro-

cardiograms during this period of hospitalization showed constant ST-segment and T-wave changes interpreted as suggestive of pericarditis. Heart size was shown to be normal roentgenographically.

Clinic visits in the fall of 1951 and in early 1952 always emphasized persistent anginal attacks, necessitating the use of glyceryl trinitrate four to five times daily and even more often at night.

The blood pressure was recorded on the first admission, in 1932, as 120/95. During the latter months of pregnancy and at the time of admission to the obstetrical service, in October, 1939, the pressure was 160/110. At the time of discharge it was 135/90. In 1947, at the time of admission to the surgical clinic because of pain in the right flank, abdomen, and both shoulders, the pressure was recorded as 140/95.

At the time of admission to the medical service in February 1948 the blood pressure levels were recorded as follows: left arm 110/80, right arm 120/80, right leg 160/110, left leg 180/100. In July 1948 it was 110/80. Later in the year it was 145/85.

In the fall of 1950, when severe precordial pain brought the patient to the medical clinic, the pressure levels were about 160/100. In the month on the medical service beginning Dec. 4, 1950, the blood pressure chart showed ranges from 110 to 160 systolic over 75 to 100 diastolic.

At clinic visits in the spring of 1951, records of blood pressure variations indicate levels of 110/80 to 170/100. On the wards in July 1951 the levels were from 110/70 to 120/90. In February and April 1952 at clinic visits the pressure was 200/100. In July it was 140/85. Severe epistaxis, controlled by packing, had occurred 12 hours before.

Abdominal Manifestations: Pain was the presenting symptom in 1932, when the patient's Vanderbilt University Hospital record was begun.

Mild pain had been noted off and on in the right abdomen and right flank for about three years. These symptoms had become more troublesome as a dull pain for six months before admission. Four days before entry to the surgical ward the patient had acute colicky pain which doubled her up and was referred to the epigastric region. It then localized in the right flank and right lower abdomen, at times referred to the right costal margin and at times radiating to the right thigh.

Nausea and vomiting occurred within two hours of the onset of pain and persisted for four days; after admission everything taken by mouth was vomited. Urinary frequency had been present for 18 months.

Examination revealed marked tenderness in the right costovertebral angle and to a lesser degree in the lower right quadrant. There was never any fever during this period of observation.

Numerous urinalysis showed a trace of 1+ level of albumin, specific gravity up to 1.026, and occasional granular, hyaline, and cellular casts, as well as 15 to 100 white blood cells and an occasional red blood cell per high-power field. There was mild leucocytosis (cell count 10,000 to 13,000).

A pyelogram of the right kidney showed no abnormality; cystoscopic study revealed cystitis and ureteritis.

Though pyelitis seemed the most likely diagnosis, circumstances led to an appendectomy, done on March 23, 1932. The pathologic report was "no microscopic lesion."

At the time of the patient's pregnancy, in 1939, there again was recurrent pain referred to the right flank. There was an occasional trace of albumin and a good concentration of the urine. Intravenous pyelograms revealed slight hydronephrosis on the right and a double ureter and pelvis on the left side.

In 1940 the patient had occasion to complain of urinary frequency, day and night. The urine showed only a 1+ albuminuria. Upon the patient's visit to the gynecology clinic, in 1945, she complained of recurrent attacks of pain referred to the right costovertebral angle, lasting for one to two days. With this would be urinary frequency and dysuria.

Recurrent and severer pain in the right lumbar area and upper abdomen brought the patient to the surgical clinic in June 1947. Nausea and vomiting were occurring immediately after meals. At times the pain was relieved by vomiting. Again it required hypodermic injections by the doctor. (Weight loss and severe pain accompanied the pain in the flank and abdomen.) Radiologic studies of the chest and gallbladder (with a contrast medium) as well as pyelograms showed no abnormalities.

Nausea, vomiting, and abdominal pain were present at the time of admission to the medical service in February 1948. The attacks of right upper quadrant pain occurred almost daily. Likewise the urinary frequency, nocturia, and dysuria continued as before. A palpable liver edge was described for the first time at this admission.

During the period of hospitalization in 1948 the patient was observed in several attacks of pain in the upper right quadrant, with a "squeezing" type of pain radiating to the back and shoulders. Nausea and vomiting accompanied these. At another time there was lower abdominal cramping pain associated with six to eight loose stools.

Gastrointestinal series, barium enema, cholecystograms, and pyelograms again showed no abnormalities. Retrograde pyelograms showed no abnormalities. Forty-eight specimens of urine were normal with one or two exceptions in a three-month period of hospitalization. Renal function was normal.

Clinic notes in the latter months of 1948 record occasional bouts of vomiting. Early in 1949 the patient had lower abdominal cramping pain with nausea and occasional vomiting. This lasted for two weeks. The urine showed a trace of albumin. No leucocytosis or fever was present.

An attack of nausea and vomiting recurred in April 1950. In December 1950 the patient complained for the first time of pain in the upper left abdominal quadrant. Tenderness was present here. This persisted after the patient's admission to the medical service on Dec. 4, 1950, and throughout the stay on the ward. Tenderness with muscle spasm was marked on palpation for the spleen, and for the first time the spleen was palpable, remaining so thereafter. (Splenic enlargement was found also on a plain film of the abdomen.) The urine continued to show a trace to 2+ level of albumin and some white blood cells and 3 to 15 red blood cells per high-power field.

The pain and tenderness in the splenic area were commented upon several times at clinic visits in the spring of 1951. The spleen remained palpable. The urine remained normal or showed only a trace of albumin.

During the hospitalization of July 1951 the patient had pain in the right flank for a time. Anorexia and at times nausea and vomiting were present. The urine was either normal or showed a 2+ albuminuria and 10 to 12 white blood cells and red blood cells per field. The liver and spleen continued to be palpable and tender.

Bouts of nausea and vomiting occurred during the fall of 1951 and early in 1952. A "sticking" sensation referred to the bladder and nocturia were complained of in February 1952. The urine showed at this time 1+ albuminuria and 20 to 30 red blood cells and 5 to 10 white blood cells microscopically as well as occasional finely granular casts. Generalized abdominal tenderness especially marked in the upper left quadrant was present at this time. The liver was tender on palpation. Diarrhea was troublesome in March 1952.

Genital Complaints: Symptoms of this type brought the patient to the gynecology clinic in 1939. Since 1937, amenorrhea had recurred lasting from two to three months at a time. Lower abdominal cramping appeared at intervals. A pregnancy of six months' gestation was the actual reason for entering the clinic in 1939.

A foul vaginal discharge led to readmission to the gynecology clinic in April 1940. Dysmenorrhea brought the patient to the clinic in February, 1945. This had been present only since the birth of her child in 1939. The pain was referred to both lower quadrants. A foul vaginal discharge again was present.

Amenorrhea was present for six months in the early part of 1948, at a time when the patient was having many and varied symptoms and signs. Menses had been reestablished regularly by the latter part of that year.

Central Nervous System Symptoms: Headaches of frontal distribution were said, at the time of the initial history (1932), to have recurred for "many" years. They were described as lasting for from one to six days, unaccompanied by nausea or vomiting.

While in the obstetrical service in 1939, the patient described two dizzy spells with short-lived diplopia in the eighth month of pregnancy.

In February 1938 it was found that the tendo achillis reflexes were absent. Position sense in the left great toe was lost. Pin-prick was interpreted as warmth over the left foot. At this time spinal fluid studies were negative.

In May 1950 the patient returned to the medical clinic because of an attack of severe right frontal and occipital headache, blurred vision, and vertigo which interfered with walking. No neurologic signs were present. The same symptoms recurred two weeks later.

In June 1951 the patient experienced an episode of unconsciousness for several minutes at home. No convulsions occurred, but numbness of the right side of the body was noted for a time. Neurologic examination a few days later showed no abnormalities. From April until July 1951 the patient complained of tinnitus and dizziness. An electroencephalogram in May 1952 gave no evidence of generalized cortical dysfunction but suggested a focal abnormality in the left frontal area.

Extremities, Symptoms and Signs: Complaints referable to the extremities brought the patient to the medical service in February 1948. For several months the patient had had numbness and pain of the hands and feet; these were present almost constantly. The paresthesias consisting of numbness and tingling had prevented the use of the hands for fine work. She felt that her sense of touch and pain were impaired. The pain in the legs was noted especially on exertion, though it might awaken her from sleep. The pain was described as "sharp and tearing" beginning in the foot, radiating up the leg to scatter into "little rockets" and lasting for one to two minutes. The paroxysmal pain might radiate at times from the extremities to the trunk. There was constant residual soreness of the feet and hands. Walking accentuated the pain.

Inflation of the blood pressure cuff produced such severe pain that after one to two minutes it caused the patient to cry out. After release of the pressure the arm became cadaveric, remaining so for 8 to 10 minutes, after which a mottled blushing was present for 15 minutes. No petechiae developed.

Burning pain of the legs continued throughout the 12-week period of hospitalization in the spring of 1948. At clinic visits during the last half of 1948 and throughout 1949 the patient commonly complained of paroxysmal pain in the legs and paresthesias in the hands and feet. At times there was cramping of the toes.

Upon her readmission to the medical service, Dec. 4, 1950, the extremities were cold and clammy. There was much pain referred to the legs. Two weeks before admission the second right toe was struck by sudden pain which radiated to the hip; the toe then turned blue and apparently was purpuric. At the time of admission it was cyanotic, cold, moist, and very tender. The patient had been free of the paresthesias of the hands and feet for quite some time. At times during this hospitalization no arterial pulsation could be felt below the popliteal arteries, again it was present in the tibial but never in the dorsalis pedis arteries.

During the spring of 1951 clinic records called attention to persistent pains in the legs; they remained cold and tender. In February and March 1952 nocturnal cramping in the thighs, legs, and hands was very troublesome.

Cutaneous Manifestations: Skin changes accompanied the paresthesias which brought the patient into the hospital in February 1948. She complained of blue areas on the legs or feet which would last only several hours. She also described "bruised spots" occurring at times. At this time the skin was said to be soft and elastic, slightly pigmented, pale to pink in color. A butterfly pattern of flushing was described on the face.

In the latter part of 1948 the patient had a pruritic rash of the legs and abdomen. Early in 1949 the legs were cold, and irregular wine-colored splotches appeared on the skin.

On April 30, 1950, a generalized maculopapular eruption involving all parts of the body, including the face, was the cause for readmission to the medical service. This appeared suddenly on that day, and by the time of admission it had become petechial and purpuric over the legs. The face showed a pronounced malar flush. (This rash had its onset four days after the appearance of a cold with nasal congestion, epistaxis, pharyngitis, and cough.) The patient was afebrile. A Rumpel-Leede test could not be continued beyond five minutes because of severe pain but was negative within this time.

There was a recurrence of a purpuric rash of the legs in July 1950.

Upon readmission to the medical service in December 1950 the patient again had a diffuse petechial rash over both lower extremities below the knees and on the inner aspects of the thighs. Within one to five minutes after the giving of tetraethylammonium chloride cyanosis and pallor of the legs disappeared and skin temperatures rose 2 to 3 degrees.

A recurrence of the malar flush was noted in March 1951. In May 1951 the left foot and leg were involved by a petechial rash.

A new type of skin lesion had appeared in January 1952. On the left shin had appeared red, hot infiltrated lesions which suggested erythema nodosum. The residua seemed to bear this out, infiltrated brownish tender areas being present at the time of a visit to the clinic. The skin of the lower extremities showed the usual mottling. In May 1952 there were ecchymotic areas on the legs and wrists; one of the toes was very tender and had an area of subcutaneous hemorrhage.

Edema: Edema of the feet and ankles, especially in the evening, was noted first in 1927, according to the record of 1932. It was observed and described when the patient was in the hospital for delivery, in 1939. Pitting edema was found during the stay on the medical service in the spring of 1948. At times it was noted at clinic visits during the latter part of 1948 and in 1949, and in the years thereafter. It has been present in 1952.

Edema of the face was a complaint in 1940; it and associated edema of the ankles lasted only a few hours. While the patient was on the medical service in 1948, edema of the face was noted. This was observed later at times on clinic visits.

Weight: A gain of 50 lb. (22.5 kg.) between the time of delivery in 1939 and the patient's visit to the gynecology clinic in 1945 was recorded. In June 1947, after a period of recurrent pain in the right flank and abdomen and vomiting, the patient complained of a 50 lb. (22.5 kg.) weight loss.

In February 1948 it was noted that in the preceding year the weight had dropped from 196 to 114 lb. (88.2 to 51.3 kg.). During the two-month period of hospitalization the weight declined from 114 to 99 lb. (51.3 to 44.5 kg.).

At a clinic visit in August 1948 the patient's weight had reached 119 lb. (53.5 kg.); by December it was 138 lb. (62.1 kg.). The following month her weight was 148 lb. (66.6 kg.). During 1949 her weight increased to 157 lb. (70.6 kg.). At the time of readmission to the medical service in December 1950 her weight was 141 lb. (63.4 kg.); at discharge five weeks later it was 132 lb. (59.4 kg.).

Fever: This was encountered for the first time in February 1948. For the first five days on the medical service a remittent temperature was present, varying from 98 to 101 degrees; for a week thereafter the range was from 98 to 100 degrees. Thereafter it was normal except for an occasional rise to 100 degrees.

The course in the hospital during December 1950 and early January 1951 was afebrile. At times in the spring of 1951 the patient was found to have low-grade fever. However, during the hospital stay in July 1951 there was no fever.

Laboratory Data.—The mass of laboratory data accumulated over 20 years of admissions to the wards and visits to the clinics of Vanderbilt University Hospital can not be detailed. Urinalyses and hematologic determinations run into many dozens.

Urinalyses have been correlated with the section on abdominal pain, because of the ever-present idea that pyelitis was the cause of recurrent pain in the right flank. Indigo carmine was excreted well at five minutes in 1948. By December 1950 specific gravities were lower than in the past. An intravenous phenolsulfonphthalein test in July 1951 revealed an excretion of 2% at 15 minutes, 5% at 30 minutes, and 10% at 120 minutes.

Hemoglobin determination at the initial admission was 15 gm. In the final period of the patient's pregnancy, in 1939, it was 11 gm., with a red cell count of 3,650,000. At the time of study in the surgery clinic, in June 1947, the hemoglobin was 11.2 gm. and the red cell count was 3,970,000.

Sometime late in 1947 the patient's blood was "low" and a transfusion was given at a hospital elsewhere.

During the hospitalization from February to May 1948, hematologic studies were performed. Bone marrow studies were nonrevealing. Twenty hemoglobin determinations varied from 9.5 to 11 gm., red cells from 2,580,000 to 4,300,000, and white cells from 9,000 to 11,000. The smears suggested hypochromic normocytic anemia. Gastric analysis revealed free acid after histamine.

By the latter part of 1948 the hemoglobin had risen to 13 gm., and in 1949 to 14 gm. This level was present at the time of admission to the medical service in May 1950. By December the hemoglobin had fallen to 10.8 gm., and it remained at this level during the month of hospitalization beginning on Dec. 4. This level persisted throughout the spring of 1951. During July 1951, while the patient was in the hospital, the hemoglobin level was 11.9 gm. A level of 11 gm. was maintained throughout the fall of 1951 and the first quarter of 1952. It then gradually fell, to reach 9 gm. in July 1952, with a packed cell volume of 32.

Leucocytosis practically never occurred. In the many blood cell counts only two elevations occurred, to 16,000 and 17,000, respectively. All others were regularly between 6,900 and 10,000.

Differential blood cell counts were not remarkable. Segmented polymorphonuclear cells usually were of the order of 70 to 80%, lymphocytes 15 to 20%, with the remainder being monocytes and occasionally an eosinophile or two. Total eosinophile counts were 91 and 19 in February 1952.

Sedimentation rates were usually between 28 and 48 mm.

Total serum proteins commonly ranged from 5.72 to 7.09, albumin 2.65 to 4.29, and globulin 2.7 to 3.7 gm. per 100 cc. Only several times was the albumin: globulin ratio 1: 1 or greater on the globulin side.

Nonprotein nitrogen values were usually in the thirties. Late in 1950 they rose to 54 to 71 mg. per 100 cc., to return to 34 mg. in March 1951. Since May 1951 no value below 51 mg. has been recorded. The level reached as high as 105 mg. in September 1951 though in April 1952 it was 66 mg.

Calcium values have always been between 9.2 and 10.5 mg. per 100 cc. Phosphorus levels have, in general, been 3 to 5 mg. per 100 cc. The highest value reported was 5.7 mg. in September 1951. Chlorides were determined a few times and found to be normal, the last, in September 1951, being 100.4 mEq. per liter. At that time the values for sodium and potassium were 152 and 5.8 mEq. per liter, respectively. Cholesterol levels were usually 200 to 300 mg. per 100 cc. Fasting blood sugar levels were always normal.

Liver function tests in February 1948 showed sulfobromophthalein (Bromsulphalein) retention of 70% at 5 minutes and 18% at 30 minutes (2 weeks later the retention was 40% at 5 minutes and 5% at 30 minutes); the alkaline phosphatase rose to 28.3 Bodansky units on March 16, dropping to 10 units seven weeks later and to 4.5 units several months later; thymol turbidity results were from 4.5 to 7 units; cephalin flocculation test was negative. In May of 1950 there was a 34% retention of sulfobromophthalein at 45 minutes. At this time the tests revealed the cephalin flocculation to be 2+ at 48 hours, a thymol turbidity 7.5 units, and an alkaline phosphatase reaction 4.6 units. In December 1950 sulfobromophthalein retention was 8% at 45 minutes. Alkaline phosphatase was reported as 10.8 and 14.8 Bodansky units in September 1951. Prothrombin levels were 100% in 1948 and 1950, and 81% in 1951.

Congo red test showed 70% in the blood at one hour in 1948.

Bleeding and clotting time were demonstrated not to be abnormal on several occasions. Clot retraction was normal. Vitamin C serum levels were 0 mg. in 1950 and 0.31 in December 1950. Rumpel-Leede tests done several times were unsatisfactory because of the intense pain due to compression of the arm. However, in December 1950 and September 1951 tests were successful, with 26 and 29 petechiae respectively.

Porphyrins and urobilinogen were not demonstrable in the urine in 1948 nor in May or December of 1950.

Occult blood in stools was demonstrated only occasionally, the tests usually being reported as negative.

Many urine cultures were done in the two decades and were consistently negative. Blood cultures on several occasions were negative. All agglutination tests for the common infections were consistently negative.

Wassermann and Kahn tests were repeatedly negative.

Arsenic could not be demonstrated in the hair or nails in 1948.

Results of Tissue Examinations.—Appendix (1932): The appendix itself was not inflamed. Numerous small arteries exhibited marked alteration (Fig. 2*A*). There was an eosinophilic fibrinoid appearance to the thickened intima, and numerous inflammatory cells, both polymorphonuclear and round cells, were seen in the vessels and adventitia.

Skin and Striated Muscle (1948): No significant changes were evident in a section of skin. The striated muscle was definitely altered, with interstitial infiltration of leucocytes and actual necrosis of muscle fibers (Fig. 2*B*). Innumerable lymphocytes and some polymorphonuclear cells were present in the wall and adventitia of a small artery in this section (Fig. 2*C*). The structure of the vessel wall was preserved.

Striated Muscle (1950): Several arteries exhibited a focal arteritis (Fig. 2*D*). There was actual necrosis of the wall of one artery, with fibrinoid material, nuclear fragments, and an extremely heavy exudation of polymorphonuclear leucocytes. The focal nature of the lesion

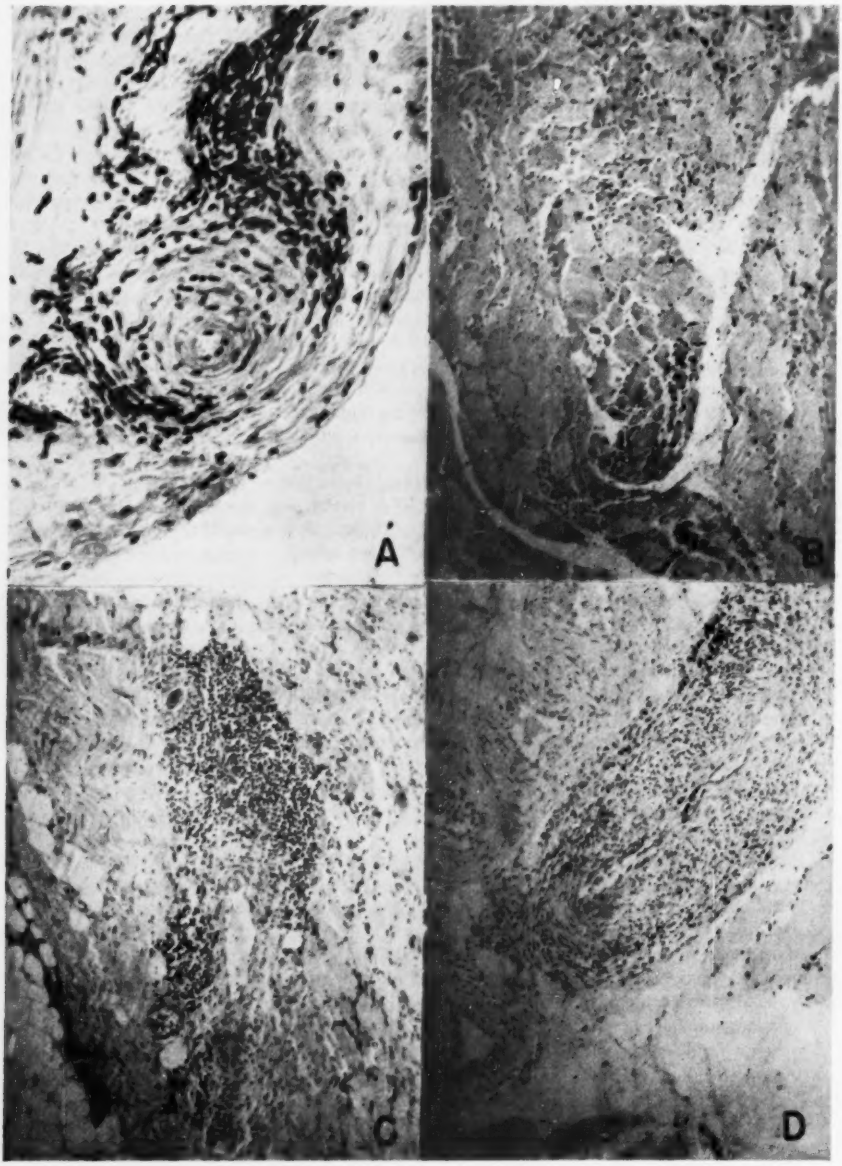

Fig. 2 (Case 3).—*A*, section of appendiceal artery (1932). The fibrinoid alteration in the wall and leucocytic infiltration in wall and adventitia are evident. *B*, section of striated muscle (1948). There is interstitial infiltration of leucocytes and round cells, and frankly necrotic fibers are seen. *C*, small artery in same section as in *B*. The exudative reaction, with round cells and some polymorphonuclear cells, is marked, but the vessel wall is structurally intact. *D*, small artery in striated muscle (1950). Fragmentation of wall, nuclear debris, and heavy leucocytic infiltration of wall and adventitia are demonstrated. An adjacent segment of artery is normal.

merits emphasis. In this instance, as well as in several others, the lesion was demonstrated by the use of multiple sections from the same tissue block, when a routine single microscopic section was interpreted as normal.

Comment.—Because of our interest in this patient we reexamined the section from the appendix removed in 1932 and now recognize the acute arteritis. Her subsequent course since the appendectomy has been one of remissions and relapses, with symptomatology referred to every system of the body. Some symptoms have been recurrent; others, such as angina and pain of peripheral nerve origin, have become permanently established.

In the patient's youth and later she had manifestations common to rheumatic fever, epistaxis and tonsillitis. An attack of arthritis in 1925, though of six months' duration with involvement of several joints, was not characteristic of rheumatic fever, because of the permanent residua in the right wrist joint. Health in childhood was impaired, if the history of inability to keep up with playmates and dyspnea on exertion are acceptable. Wheezing was described in these attacks of dyspnea until in her twenties, when this characteristic was lost.

The history of exertional dyspnea almost all her life, paroxysmal nocturnal dyspnea for more than 20 years, increasing in intensity and frequency in the past five years can not be accepted as evidence of long-standing decreased myocardial reserve in the absence of congestive failure before now. It is difficult to say whether this has represented bronchial asthma, though probably so, at least in childhood. At times it may have represented arteritis in the pulmonary vascular bed. In the past five years it may have been an anginal equivalent. Precordial pain on exertion for two decades, with frequent and severe angina in the past five years, points to coronary artery disease. Some of these attacks with attendant shock have been observed and are dramatic.

The many bouts of pain in the right flank attended by albuminuria, casts, and white and red cells in the urine, with consistently negative cultures, are indicative of vascular renal disease. In recent years, just as the persistent and severe angina points to encroachment on the coronary bed, so too does the gradual faliure of renal function in terms of azotemia and rising blood pressure indicate a diminishing renal blood supply. The recurrent attacks of abdominal pain, usually accompanied by nausea and vomiting and occasionally by diarrhea, suggest mesenteric, visceral, or peritoneal vascular disease. Muscular spasm of the gut, resulting from focal vascular disease so well illustrated in the appendiceal artery in 1932, could well account for periodic pain. Hepatomegaly and splenomegaly were to be anticipated eventually in the face of recurrent arteritis. All this is compatible with the clinical picture of periarteritis nodosa.

Less clearcut, but suggestive symptoms of central nervous system disease appeared.

Symptomatology duplicating that of the involvement of peripheral nerves as may occur in periarteritis nodosa, with attendant vasomotor disturbances and Raynaud-like phenomena, has been prominent in the past four years. The muscular pain, the edema of ankles and face, the macular and erythematous rashes of the past four years could well establish a working diagnosis of dermatomyositis. Yet the recurrent petechial rash, the butterfly rash on one occasion, with the renal disease, pericarditis, arthralgias, and varying electrocardiographic disturbances might at any time lead to a diagnosis of disseminated lupus.

In this case we have had the opportunity to examine tissue upon three different and widely separated occasions. Sections of the appendix removed 18 years prior to the last biopsy revealed numerous inflamed arteries in an otherwise normal organ. The vascular lesion varied from an exudative one, with numerous round cells and histiocytes in the adventitia, to an actual fibrinoid change within the walls of one small artery, again with the surrounding cellular exudate. We think the arteritis is of significance in this case, even though Plaut [8] has described similar though less widespread lesions of the arteries in appendices removed incidental to other abdominal operations.

In the biopsy 16 years later (1948) a definite myositis was found and again a vascular lesion was noted. In this instance the arterial reaction was purely exudative. There was no structural change in the arterial wall, but the exudation of segmented and round cells and large mononuclear phagocytes was striking.

An intensely destructive process, best classified as a necrotizing arteritis, was found in the biopsy of striated muscle some two years later (1950). Fragmentation of the media, fibrinoid alteration and an exudate composed largely of polymorphonuclear cells were present.

In this case at various times we have seen separate and distinct morphological stages of arterial inflammation. If one accepts the premise that this type of lesion is a result of hypersensitivity, such variations in appearance at different times may represent the resultant of the degree of reactivity of the host upon exposure to an antigen, variable in quantity or possibly in quality.

Thus this patient, with a history of focal arterial disease of two decades and more, provides a clinical picture difficult to classify by any criteria into any of the syndromes we recognize. Yet that she had recurrent focal arterial disease can not be denied either upon clinical or pathologic grounds.

What this patient's future course will be is difficult to predict with accuracy. But the past five years of increasing evidence of coronary and renal disease suggest that the story may draw to a close in the not too distant future.

CONCLUSIONS

The cases which have been considered have shown the variability of the clinical course of diffuse arteritis. Rapidly progressing necrotizing arterial disease leading to fatal termination may occur if the arteritis is of acute onset, representing a generalized insult to the vascular system. If the process is a recurring one with remissions and exacerbations the pathologic change may vary from acute necrosis to healing with recanalization.

The course of a disease characterized by diffuse arteritis and extending over a period of more than 20 years has been presented. Remissions and exacerbations have been present and there is proof that arterial disease of varying degrees and types was present during this period. Biopsy studies emphasize the focal nature of the arteritis under discussion, since often numerous sections are needed to demonstrate the essential lesions.

Because of its great variability the clinical course might well have been classified as dermatomyositis upon one occasion, as disseminated lupus erythematosus on

8. Plaut, A.: Asymptomatic Focal Arteritis of Appendix: 88 Cases, Am. J. Path. **27**:247 (March-April) 1951.

another occasion, and as periarteritis nodosa on still another occasion. In fact the great variety of manifestations of disease throughout a period of over 20 years precludes its designation as any single type of arteritis now classified.

It may be anticipated that a benign process with partial or complete healing of arterial lesions may result in prolonged illness in some patients and actual recovery in others.

ADDENDUM

(Subsequent to the completion of this paper and its acceptance for publication, it appeared that the course of this patient's illness was drawing to a close. Publication was postponed for the additions which follow.)

The patient was seen at approximately monthly intervals in the outpatient department from May 1952 until April 1953, when she was admitted to the hospital for the last time.

Certain of the symptoms, which had been prominent before, continued with varying frequency and severity. Epistaxis recurred frequently requiring nasal packs at times. Angina of varying severity recurred often, usually with radiation to shoulders and arms. Glyceryl trinitrate was used from one to six times daily. Pain in the arms and legs was troublesome at times. Purpuric rashes involving the fingers occurred occasionally. Paresthesia and a tendency to drop things was referred to the right hand for some days in November 1952. Nausea and vomiting occurred almost daily or every other day after early January 1953. The patient noted twitching of the muscles during March 1953.

The main physical abnormalities were a blood pressure varying from 140/85, in July 1952, to 200/110, in January 1953, usually at about 180/100; a persistent soft systolic murmur; purpuric areas in the skin, and a palpable splenic tip on one occasion.

Laboratory determinations during these months showed a 2+ albuminuria, hemoglobin values of about 10 gm., packed cell volume values of 30, and normal results of liver function tests on one occasion. The nonprotein nitrogen values were 56 mg. in November and 116 mg. in January; the phosphorus was 6.6 mg. in January. An electrocardiogram in January showed nonspecific ST-T wave changes.

Seventh Hospital Admission.—The patient was admitted to Vanderbilt University Hospital for the last time on April 23, 1953, after appearing in the clinic weak, breathless, and showing marked pallor.

At the time of examination the skin appeared pale and waxen; ecchymoses were present on the extremities. One petechial hemorrhage was found in the right conjunctiva. The heart seemed to be enlarged to the left. A harsh blowing systolic murmur was heard over the whole precordium; occasional premature contractions were present. There was generalized tenderness of the abdomen and flanks. The liver was palpable, smooth and tender, 2 cm. below the costal margin. All joints were slightly painful and tender. The blood pressure was 180/100.

Laboratory data on admission showed a 3+ albuminuria, hemoglobin 5 gm., and a packed cell volume of 15%, a white cell count of 4,000, and a normal differential picture. The nonprotein nitrogen was 120 mg., calcium 6.8 mg., phosphorus 7.6 mg. per 100 cc., and CO_2 12.6 mEq. per liter. Total serum protein was 5.2, albumin 3.8, and globulin 1.4 gm. per 100 cc.

The clinical course was one of developing and progressive congestive failure and uremia, to end in death after one month.

There developed moisture at the lung bases, edema, pleural effusion, and ascites. Digitalization was instituted. A precordial friction rub appeared about two weeks after admission.

The uremia was manifested by persistent vomiting, early occasional muscular twitching, and progressive stupor. The patients showed psychotic reactions; recurrent convulsive seizures developed five days before death, and eventually uremic frost was demonstrated.

The blood pressure ranged from 140/85 to 185/105. Six electrocardiograms always showed ST-T wave changes.

Hemoglobin and packed cell values varied with transfusions. The white cell count varied from 6,000 to 18,000. Total serum proteins dropped to 4.1, albumin 2.9, and globulin 1.2 gm. per 100 cc. Two attempts to demonstrate lupus erythematosus cells failed. Prothrombin time was 81%; clotting time was four minutes. The nonprotein nitrogen level rose with fluctuations to a final

level of 272 mg. per 100 cc.; the calcium ranged from 6.2 to 8.7 mg.; phosphorus rose to a final level of 12.7 mg. The numerous electrolyte determinations both before and during therapy for electrolyte imbalance are not pertinent.

Six transfusions, of 500 cc. each, were given. Corticotropin (ACTH), 20 units intravenously, was given on each of four successive days without influencing the course.

The patient died after a convulsion on May 26, 1953. Autopsy was performed.

Autopsy.—Gross Examination: The external examination revealed no significant changes from normal. A rather diffuse area of hemorrhage, some 7 cm. in diameter, was encountered in the rectus abdomini muscle.

Serosal cavities. Clear brownish fluid was found in the amounts of 400 cc. in the abdomen, 200 cc. in the right pleural cavity, and 500 cc. in the left pleural cavity. A few fibrous pleural adhesions were noted. The pericardial cavity was almost obliterated by thin, easily broken fibrous adhesions. No fibrinous exudate was identified grossly.

Heart and arteries. The heart weighed 440 gm., with the moderate enlargement due predominantly to hypertrophy of the left ventricle. The myocardium was remarkably flabby, and throughout the wall of the left ventricle there were focal white scars varying from a few millimeters to 1.5 cm. in the broadest diameter. No fresh areas of necrosis were encountered. The valves were entirely normal, and the coronary arteries were notably free of atherosclerotic change in view of the focal scarring found in the left ventricle. Only minimal arteriosclerosis was present in the aorta, and the renal vessels were entirely free of atheromata. A 2 cm. segment of the superior mesenteric artery close to its origin showed concentric fibrous thickening of its wall, with a narrowed lumen.

Lungs. There was moderate edema of both lungs, and areas of focal atelectasis were encountered. No significant bronchial or pulmonary vascular changes were found.

Gastrointestinal tract. A few petechial hemorrhages were present in the mucosa of the large bowel; there were no other remarkable findings.

Liver. There was focal capsular scarring over the surface, and central congestion was prominent on examination of the cut surfaces. There were no focal lesions. The gallbladder was normal except for the presence of two large brown faceted stones, each some 3 cm. in diameter.

Spleen. The spleen was moderately enlarged and weighed 170 gm. There were tiny areas of fibrous thickening of the capsule over the surface. The pulp was soft and dark red. A few hard tubercles were seen.

Pancreas. The pancreas was normal except for diffuse increase in consistency.

Adrenal glands. The adrenal glands were thought to be somewhat larger than normal, and the cortex measured about 2 mm. in thickness.

Kidneys. The kidneys were markedly altered from the normal (Fig. 3). The right kidney was small, weighing only 30 gm. The capsule of this organ stripped with slight difficulty, revealing a coarse uneven granularity with a few petechial hemorrhages. The cortex measured only 3 mm. in width, with obliteration of the cortical striations. The pyramids showed no scarring or distortion, and the pelvic mucosa was normal in appearance.

The left kidney was in general very similar to the right except that it was larger, weighing 70 gm. The nodular surface and cortical scarring with preservation of the pyramids and normal pelvic mucosa were striking. In both kidneys the arcuate and small arteries were thickened and prominent, though, as stated above, the larger renal vessels were entirely normal.

Ureters. There was reduplication of the left ureter, with a double pelvis and a double orifice in the urinary bladder.

Internal genitalia. No significant abnormalities were encountered in examination of the genitalia.

Central nervous system. The arteries at the base of the brain were thin and translucent. There was mild flattening of the convolutions, suggesting cerebral edema. No additional lesions were found on sectioning the formalin-fixed brain.

Microscopic Examination: Abdominal muscle. A section of the hemorrhagic rectus muscle revealed diffuse coagulative necrosis of the wall of a small artery, with dilation and a surrounding heavy exudate of polymorphonuclear leucocytes (Fig. 4*A*).

Heart. There was a thin layer of fibrin on the pericardium, with a few associated round cells. One very small area of acute myocardial necrosis was found, and several focal scars with collapse of the stroma were noted. Many small arteries had thickened walls. A section of aorta was not remarkable.

Lungs. Focal areas of atelectasis and a few small clumps of intra-alveolar fibrin constituted the only marked changes in the lungs. The bronchi seemed a little dilated, and the vessels were normal.

Gastrointestinal tract. There were no significant lesions found in numerous sections of esophagus, stomach, and small and large intestine. The submucosal arteries of the intestine were moderately thickened.

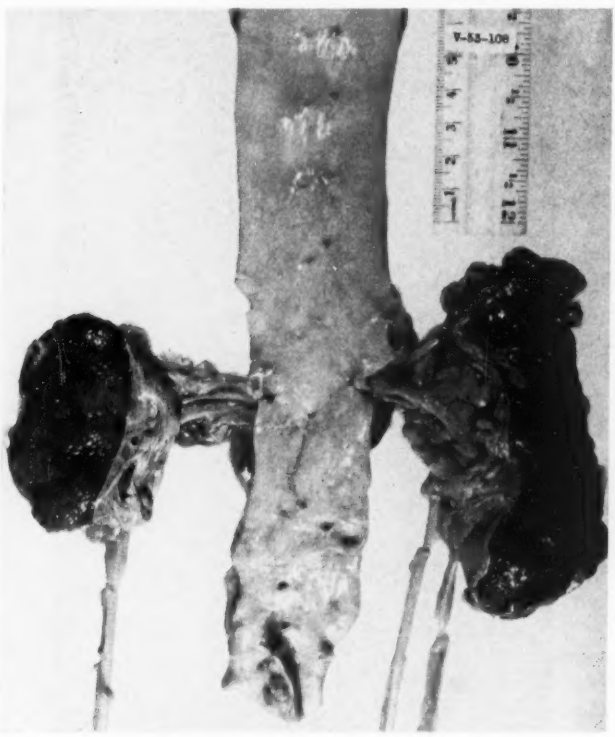

Fig. 3 (Case 3).—Coarse granularity and petechial hemorrhages in the cortex of the small kidneys. The lack of arteriosclerotic change in aorta and renal arteries is evident.

Liver and gallbladder. The capsule was slightly thick and fibrous. The lobules were well preserved, and no change was seen in the triads. There was moderate intracellular accumulation of fat in the periportal areas. The gallbladder wall showed numerous chronic inflammatory cells, and the arteries of the gallbladder wall were thick and tortuous, with the lumens quite narrow due to proliferative reaction in the walls of the vessels.

Spleen. The sinusoids were engorged with red cells. The over-all architecture was not altered. No "onion-skin" thickening of the splenic arteries was apparent.

Pancreas. There was a diffuse mild increase in connective tissue, with no change in vessels or epithelial structures.

Adrenal glands. Aside from some scarcity of cortical lipids, the adrenal glands were normal.

Kidneys. Sections from the two kidneys revealed an entirely similar picture (Fig. 4*B* and *C*). The pelvis and medullary structures were relatively normal, though the pyramids were small.

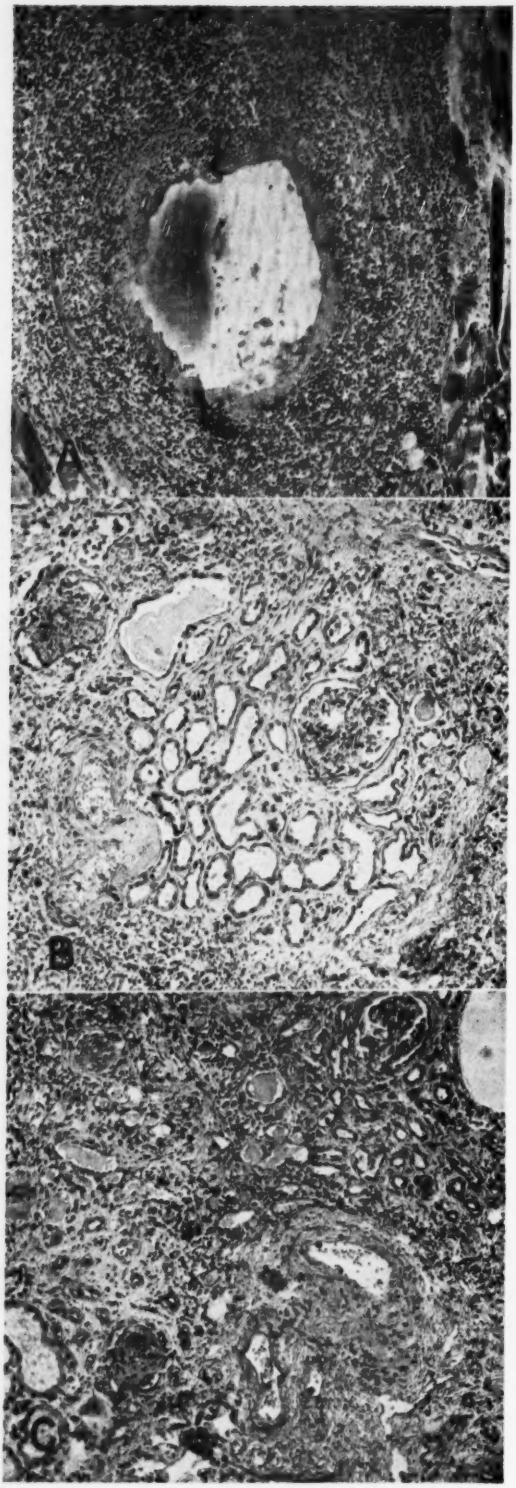

Fig. 4 (Case 3).—*A*, necrotic dilated small artery in the rectus abdominis. The heavy collar of inflammatory cells is composed primarily of neutrophiles. *B*, tortuous thickened artery in renal cortex, with diffuse scarring, adhesions, and early fibrosis in glomerular tufts. *C*, extensive fibrosis and adhesions in glomeruli and arterial changes present throughout both kidneys.

The cortex exhibited diffuse interstitial fibrosis, with numerous round cells present. Many groups of tubules were atrophic, containing hyaline casts, while hypertrophied tubules were seen focally in association with large glomeruli. Every glomerulus was altered, with the changes varying from adhesions between tufts and capsule to complete obliteration by fibrous tissue proliferation. The cortical arteries were most striking. These vessels, including arcuate and interlobular arteries, exhibited diffuse fibrous thickening of their walls and were extremely tortuous. Focal areas of more marked thickening were found. The arterioles were not significantly altered.

Numerous other tissues, including those of the central nervous system, neck organs, skin, and synovium of right shoulder joint, were examined histologically without demonstration of lesions pertinent to the subject under discussion.

Comment.—The only instance of acute necrotizing arteritis demonstrated by autopsy was in a section of hemorrhagic rectus abdominis muscle. This lesion was comparable in severity and type with those found on a previous occasion (Figs. *2D* and *4A*). Though a careful search was made in many tissues for examples of healing arterial lesions, none was found. Thickened small arteries were conspicuous in the heart, gallbladder, intestinal tract, and kidneys. It was believed that the small focal areas of scarring in the heart were best explained on the basis of remote occlusions of small arteries, presumably due to lesions of these vessels of the type demonstrated in other sites and on other occasions in this patient. As noted previously, the coronary arteries were conspicuously free of atheromatous change.

The kidneys were of especial interest, because of the progressive renal failure leading to death and the rather unusual appearance of these organs at the time of autopsy. There was a diffuse loss of cortical substance and rather coarse nodularity of the stripped surfaces. Microscopically practically no normal glomeruli were found, with capsular adhesions in some and fibrous obliteration having occurred in the remainder. It was believed that on the basis of the gross and microscopic appearance of the kidneys the basic lesion would best fit into the category of chronic glomerulonephritis. An attempt was made to explain the renal cortex changes on the basis of remote arterial lesions involving vessels of the arcuate and interlobular type. It was believed that demonstration of definite old healed occlusions in these arteries would be necessary to substantiate this hypothesis. Accordingly, serial sections were cut and examined, and the thickened arteries were followed outward in the cortex. Though minute scars were found in the walls of the small arteries, it was impossible to demonstrate any areas of complete occlusion or of definite recanalization. However, it is possible that the rather unique renal lesions may have arisen on the basis of remote arteritis with atrophy of the corresponding area of the cortex, with subsequent resolution of the arterial lesions to the point that they can not be recognized as such at this much later date.

Dr. Thomas C. Delvaux performed the autopsy in Case 3, which enabled us to evaluate satisfactorily the microscopic changes.

THEORY OF THYROID HORMONE ACTION

Conclusions Derived from Differences in Effect of Sodium *l*-Thyroxine, Sodium *d*-Thyroxine, Triiodothyronine, and Potassium Iodide on Uptake of Radioactive Iodine by Thyroid Gland of Normal Human Subjects

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STUDIES of synthetic sodium *l*-thyroxine demonstrate that as an oral medication in dosage of 0.5 mg. or less daily it is calorigenic and clinically active.[1] In similar dosage it has been shown to reduce the uptake of radioactive iodine.[2] Triiodothyronine, recently identified, synthesized, and demonstrated in human serum,[3] also has been shown to be clinically effective [4] and to be several times as potent as thyroxine.[5]

Curiosity as to the possible effect of sodium *d*-thyroxine led us to carry out tests with this substance. It was difficult to obtain. Dr. Leonard Ginger, of the Baxter Laboratories, Inc., Morton Grove, Ill., the source of the levo form used in our clinical studies, produced it for us. It has already been demonstrated by Greer [6] that inorganic iodine in amounts equal to that in these medications has no effect upon uptake of radioactive iodine. We have, however, carried out a few tests at four-dose levels with iodide, and the results provide some interesting suggestions for further work.

This is a report on the effect of these medications on the 24-hour uptake of a tracer dose of radioactive iodine [7] before and at the end of a week of oral medication. The serum protein-bound iodine was also determined.

From the University of Southern California, School of Medicine, Department of Medicine, and the Los Angeles County General Hospital.

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2. Morgans, M. E.; Oldham, A. K., and Trotter, W. R.: The Effect of Exogenous Thyroxine on Radiodine Uptake in Normal Subjects and in Cases of Thyrotoxicosis in Remission, J. Endocrinol. **8**:250 (July) 1952.

3. Gross, J., and Pitt-Rivers, R.: The Identification of 3:5:3′ L-Triiodothyronine in Human Plasma, Lancet **1**:439 (March 1) 1952.

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5. The triiodothyronine used in these studies was synthesized by the Glaxo Laboratories and provided through the courtesy of Dr. Arthur Heming, of Smith, Kline & French Laboratories.

6. Greer, M. A.: The Effect on Endogenous Thyroid Activity of Feeding Desiccated Thyroid to Normal Human Subjects, New England J. Med. **244**:385 (March 15) 1951.

7. Radioactive iodine received from the Atomic Energy Commission, Oak Ridge, Tenn.

PROCEDURE

The subjects were normal volunteers occupied with their usual activities as medical students or laboratory workers. Blood was drawn for serum protein-bound iodine determinations, and about 5 μc of carrier-free radioactive iodine was given. An identical tracer dose was set aside for use as a dummy. Twenty-four hours later the concentration of I^{131} was measured with a Geiger counter. The percentage of uptake was computed by comparison of the thyroid count with the dummy count. The subjects were then provided with medication to be taken once a day for a week. On the sixth day of the week blood was drawn for the second protein-

TABLE 1.—*Sodium Levothyroxine* *

Patient	Protein-Bound Iodine, γ per 100 Cc. A	B	C	I^{131} Uptake, % D	E	F	G	H †	I	J
Dose 0.025 mg.										
F. C.	5.2	5.0		16.7	26.0					
A. M.	5.9	5.5		14.9	13.0					
R. P.	4.9	5.7	+0.4	30.1	28.5	+ 1.87	+ 9	±17	ns ‡	ns
J. A.	5.5	6.4		18.0	11.9					
S. K.	4.8	5.7		21.0	29.6					
Dose 0.050 mg.										
L. B.	5.6	5.2		14.3	12.9					
M. B.	6.4	5.2		22.8	14.5					
M. T.	5.2	4.6	−0.6	17.4	18.6	− 4.65	−18	±12	ns	ns
T. T.	4.5	4.2		32.3	22.2					
Dose 0.100 mg.										
D. H.	5.8	7.0		23.7	21.5					
P. D.	5.0	5.0		23.0	22.1					
R. M.	4.9	4.6		18.8	12.0					
D. T.	5.1	5.5	+0.1	13.9	13.0	− 7.10	−29	±10	<0.1	<0.1
R. A.	5.5	6.0		31.6	22.6					
J. M.	6.2	6.0		24.7	17.4					
H. B.	5.7	5.4		27.0	4.0					
Dose 0.150 mg.										
R. G.	4.7	5.6		20.0	12.4					
V. L.	4.4	5.3		16.2	14.4					
P. D.	4.5	4.6	+0.5	26.1	16.2	− 6.56	−29	± 5	<0.1	<0.1
C. B.	3.9	3.8		17.7	13.7					
R. E.	4.3	5.4		29.0	19.5					
Dose 0.200 mg.										
E. B.	4.6	7.1		28.0	20.7					
Dose 0.500 mg.										
B. B.	4.5	...		37.8	27.2					
R. R.	5.2	6.5		25.6	7.1					
H. L.	5.0	6.3		19.9	8.3					
L. F.	5.5	6.3		24.6	10.8					
A. V.	4.3	5.8	+1.7	16.6	7.2	−12.6	−52	± 4	<0.01	<0.01
H. B.	4.3	7.5		22.8	7.3					
D. W.	5.3	7.8		28.0	17.8					
R. G.	...	...		25.0	15.3					
P. D.	4.3	6.8		26.0	12.6					
D. T.	6.0	6.9		23.0	9.9					

* A, protein-bound iodine before medication; B, protein-bound iodine on sixth day of medication; C, average difference between protein-bound iodines; D, uptake before medication; E, uptake on seventh day of medication; F, average difference between uptakes; G, average percent of change; H, standard error of the mean; I, P value for D — E; J, P value for placebo (Table 5) — F.

† Standard error of the mean $= \sqrt{\frac{\Sigma d^2}{n(n-1)}}$

‡ Not significant.

bound iodine determination. After careful measurement of the amount of I^{131} remaining in the thyroid, a second tracer dose, of about 7.5 μc was given, and 24 hours later, on the seventh day of medication, the percent uptake of the second tracer dose was determined.

This schedule was followed throughout these studies, varying only in the type and amount of medication.

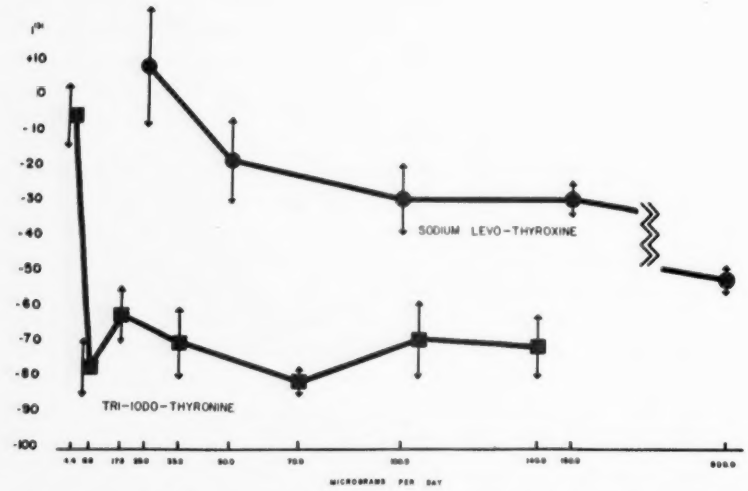
Sodium *l*-thyroxine was used in dosages from 0.025 to 0.05 mg., triiodothyronine in dosages from 0.004 to 0.140 mg., sodium *d*-thyroxine in dosages from 0.100 to 0.500 mg., and potassium iodide in dosages from 0.420 to 4.200 mg. The placebo was made up of lactose and was used in the same way.

The tests, involving 26 subjects, were repeated without medication on the same person after an interval of 42 days or longer.

It is important to note for future comparisons that the blood was drawn for the protein-bound iodine determinations and the tracer given and counted within a few hours after ingestion of the medication, on the sixth and seventh day of treatment.

RESULTS

The 25 γ daily dose of sodium *l*-thyroxine (Table 1) produced no reduction of uptake; the reduction produced by 50 γ is questionable. One hundred micrograms and 150 γ have a significant effect. The second uptake is about three-quarters of the first uptake. At 500 γ, or 0.5 mg. dosage, the depression is greater, the second uptake being about half of the first. Great individual variation, indicating, presumably, a variation in pituitary susceptibility to this treatment, is evident. The quantitative comparison of thyroxine with triiodothyronine (Figure) indicates that there



Percent depression of I^{131} uptake in 67 normal human subjects given oral medication for seven days. Circles connected by a line represent sodium *l*-thyroxine curve. Squares connected by a line represent triiodothyronine curve. Arrows indicate the standard error of the mean. Vertical scale indicates percent depression of I^{131} uptake. Horizontal scale indicates medication.

is a significant effect of thyroxine on uptake of radioactive iodine in dosages less than those having the maximal result; i. e., the effect is gradual.

Four micrograms of triiodothyronine daily by mouth for one week had no effect on the radioiodine uptake in these normal subjects measured at 24 hours. Eight micrograms had a maximal effect (Table 2). All the higher doses tested had a depressing action of the same magnitude. It would appear that the triiodothyronine was more than 5 times, and perhaps 10 times, as effective as sodium *l*-thyroxine in this action in terms of weight of medication given once a day by mouth for one week. The quantitative comparison of the effect of thyroxine with the effect of triiodothyronine indicates that the latter has a maximal action in the lowest effective dose.

This comparison is illustrated in the Figure. The abrupt descent of the triiodothyronine curve from the negligible effect of 4 γ, 5% depression, to the full effect of 8 γ, causing 37% depression, is striking. The depression of uptake caused by sodium *l*-thyroxine produces a curve marked by a slight rise with the first dose and a gradual effect, indicated by an 18% depression, with the second dose; 29% depression occurs with the next two dosages, and 52% depression with the highest

TABLE 2.—*Triiodothyronine* *

Patient	Protein-Bound Iodine, γ per 100 Cc. A	B	C	I^{131} Uptake, % D	E	F	G	H †	I	J
Dose 0.0044 mg.										
R. B.	4.5	3.9		12.4	9.9					
C. F.	6.0	4.9		10.3	9.6					
H. F.	4.8	5.1		31.2	26.9					
D. R.	5.4	4.0		15.7	19.9					
T. S.	3.9	3.8	+0.2	17.2	14.2	− 1.85	− 5	± 9	ns ‡	ns
V. H.	3.4	4.7		25.4	17.2					
P. G.	4.3	6.1		11.5	15.7					
R. S.	2.9	4.4		29.1	20.7					
P. S.	5.8	...		15.1	17.1					
Dose 0.0088 mg.										
M. L.	4.6	3.9		18.8	2.7					
M. Mc.	6.5	4.7		31.2	4.2					
C. R.	4.8	3.5	−1.1	31.6	5.9	−21.14	−77	± 6	<0.001	<0.001
G. R.	4.2	3.0		40.2	15.9					
H. S.	3.6	2.9		18.8	6.2					
Dose 0.0175 mg.										
M. A.	4.7	4.3		22.0	13.3					
R. E.	5.5	4.4		26.9	15.7					
T. G.	5.0	4.0	−0.7	21.0	2.3	−12.41	−62	± 8	<0.001	<0.001
R. G.	5.1	4.4		14.5	7.0					
M. N.	5.0	4.1		21.3	4.6					
D. P.	4.0	4.0		16.0	4.3					
Dose 0.035 mg.										
B. S.	4.2	4.2		17.0	2.7					
R. G.	4.6	3.4	−1.3	23.0	5.5	−13.9	−70	±10	<0.001	<0.001
R. P.	5.4	2.7		20.0	10.0					
Dose 0.070 mg.										
C. S.	5.0	3.0		18.0	4.0					
E. A.	5.7	5.2	−0.4	28.0	3.1	−21.3	−81	± 4	<0.001	<0.001
M. A.	3.8	5.0		20.0	5.0					
Dose 0.105 mg.										
P. S.	4.0	4.9		13.0	6.7					
R. S.	4.0	3.9	−0.2	32.0	8.9	−13.4	−69	±11	<0.005	<0.001
F. R.	4.4	2.9		13.0	2.0					
Dose 0.140 mg.										
M. F.	5.8	4.7		18.9	1.7					
A. L.	6.4	4.9		19.4	6.5					
V. L.	5.3	5.7	−0.6	39.0	5.4	−14.94	−71	± 9	<0.001	<0.001
R. M.	4.6	5.1		14.0	8.6					
R. D.	4.2	3.2		19.0	4.3					

* A, protein-bound iodine before medication; B, protein-bound iodine on sixth day of medication; C, average difference between protein-bound iodines; D, uptake before medication; E, uptake on seventh day of medication; F, average difference between uptakes; G, average percent of change; H, standard error of the mean; I, *P* value for D − E; J, *P* value for placebo (Table 5) − F.

† Standard error of the mean = $\sqrt{\frac{\Sigma d^2}{n(n-1)}}$

‡ Not significant.

dose used. It is probable that this last effect is not maximal, but the full milligram dose was not used, because of clinical reasons.

The findings with sodium *d*-thyroxine (Table 3) are similar to those with sodium *l*-thyroxine. With a dose of 100 or 150 γ a day the average depression is similar to, but somewhat less than, that with the same dose of *l*-thyroxine. The absolute differ-

TABLE 3.—*Sodium dextrothyroxine* *

Patient	Protein-Bound Iodine, γ per 100 Cc. A	B	C	I^{131} Uptake, % D	E	F	G	H †	I	J
Dose 0.100 mg.										
M. C.	5.7	5.2		21.4	15.6					
M. M.	6.3	5.8		32.2	27.9					
R. H.	5.7	5.6		13.2	11.0					
— C.	5.3	5.5	—0.2	14.3	12.3	— 5.15	—20	± 2	ns ‡	ns
S. C.	7.2	6.5		44.7	33.8					
M. C.	5.3	5.7		23.3	17.6					
Dose 0.150 mg.										
W. M.	5.0	5.4		17.6	15.1					
J. G.	4.6	5.3		20.8	20.7					
D. P.	4.3	4.7		14.7	12.7					
E. C.	5.2	6.6	+0.2	17.4	12.8	— 2.87	—17	± 5	ns	ns
H. K.	6.2	5.3		15.8	10.6					
K. E.	5.0	4.5		17.7	14.9					
M. F.	4.8	4.3		14.1	18.6					
Dose 0.500 mg.										
P. H.	5.7	6.0		37.6	23.7					
G. R.	4.7	4.5		32.1	23.9					
L. N.	5.4	4.3		16.3	10.4					
W. McC.	5.2	5.0		19.2	19.2					
J. P.	5.4	5.0		27.1	19.1					
G. W.	4.3	6.6		19.6	11.8					
M. C.	4.5	6.4		21.1	3.1					
M. M.	5.7	5.7	—0.1	33.2	6.7	—10.24	—41	± 6	<0.01	<0.01
R. H.	5.4	5.4		12.3	8.8					
M. B.	4.2	5.4		30.4	15.6					
D. B.	...	...		15.8	3.3					
L. M.	6.4	7.1		29.5	25.5					
R. A.	5.5	4.7		33.3	21.3					
M. B.	4.2	4.0		20.0	12.0					
N. C.	5.2	4.7		23.5	16.8					
D. G.	5.5	4.7		21.0	11.8					

* A, protein-bound iodine before medication; B, protein-bound iodine on sixth day of medication; C, average difference between protein-bound iodines; D, uptake before medication; E, uptake on seventh day of medication; F, average difference between uptakes; G, average percent of change; H, standard error of the mean; I, *P* value for D — E; J, *P* value for placebo (Table 5) — F.

† Standard error of the mean = $\sqrt{\frac{\Sigma d^2}{n(n-1)}}$

‡ Not significant.

TABLE 4.—*Potassium Iodide*

Patient	Protein-Bound Iodine, γ Per 100 Cc. A	B	C	I^{131} Uptake, % D	E	F
Dose 0.42 mg.						
J. M.	7.2	6.1		28.0	24.0	
R. S.	9.0	7.7	—1.2	27.0	28.0	—1.5
Dose 1.26 mg.						
L. L.	5.4	3.9		16.2	11.4	
Dose 2.1 mg.						
H. B.	...	6.4		27.0	11.0	
J. O'N.	5.2	4.2		19.8	12.3	
F. P.	6.5	4.3	—1.33	23.3	21.1	—6.77
J. H.	6.1	4.0		18.3	14.5	
R. J.	4.6	4.6		9.8	5.5	
Dose 4.2 mg.						
D. B.	5.8	5.9		19.0	9.0	
A. G.	6.0	4.7	—0.6	29.0	12.0	—8.5

* A, protein-bound iodine before medication; B, protein-bound iodine on sixth day of medication; C, average difference between protein-bound iodines; D, uptake before medication; E, uptake on seventh day of medication; F, average difference between uptakes.

ence in uptake, however, is so small that a significant change cannot be demonstrated. This may, in part, be the result of the inaccuracy of the external neck count method of uptake determination.

At the 0.5 mg. level, however, the *d*-thyroxine appears to be nearly as effective as the levo form in this regard. A contamination of the dextro material with the levo form of the chemical would account for some, but not all, of the depressing

TABLE 5.—*Placebo (Lactose)* *

Patient	Protein-Bound Iodine γ Per 100 Cc. A	B	C	I^{131} Uptake, % D	E	F	G	H †
P. L.	4.2	4.7		23.2	29.5			
M. L.	4.7	5.3		26.0	23.8			
M. B.	4.9	4.6		32.2	26.7			
D. B.	4.2	3.8		24.4	18.0			
E. B.	5.4	5.1		24.4	16.8			
R. G.	4.2	4.9		26.4	20.0			
J. M.	4.4	4.9	−0.09	21.2	23.7	−2.5	−10	±7
A. M.	3.7	4.2		16.8	12.8			
A. G.	3.9	3.9		21.2	17.4			
D. T.	4.3	4.0		19.5	12.4			
W. R.	4.7	4.3		29.6	31.0			
L. C.	3.8	3.6		11.3	17.8			
C. S.	3.1	3.4		28.3	21.9			
Two control values on same person (2-mo. to 1-yr. intervals)								
M. G.	3.2	4.2		15.8	24.4			
A. G.	6.0	3.9		29.0	21.0			
M. B.	4.2	4.9		20.4	32.2			
R. H.	5.4	5.7		12.3	13.2			
M. M.	5.7	6.3		33.2	32.2			
M. C.	4.5	5.3		21.1	23.3			
E. B.	4.6	5.4		28.0	24.0			
R. G.	4.9	4.2		25.0	26.4			
P. D.	4.3	4.5		26.0	26.1			
H. B.	5.4	5.7		27.0	23.0			
J. M.	7.2	6.2		28.0	24.7			
D. T.	4.3	5.1		19.5	13.9			
A. M.	5.0	5.9		18.0	14.9			
V. C.	5.0	4.4	+0.10	16.2	12.7	+0.1	+ 3	±9
M. F.	5.8	4.8		18.9	14.1			
C. S.	4.0	3.1		18.0	28.3			
R. P.	5.4	4.9		26.0	30.1			
R. G.	4.6	4.7		23.0	20.0			
D. P.	4.0	4.3		16.0	14.7			
R. G.	5.1	4.2		14.5	26.4			
R. E.	5.5	4.3		26.8	29.0			
G. R.	4.2	4.7		40.2	32.1			
M. C.	4.6	5.7		18.8	21.4			
P. S.	4.0	5.8		13.0	15.1			
R. S.	3.0	2.9		32.0	29.1			
R. S.	4.1	4.6		26.1	25.5			

* A, protein-bound iodine before medication; B, protein-bound iodine on sixth day of medication; C, average difference between protein-bound iodines; D, uptake before medication; E, uptake on seventh day of medication; F, average difference between uptakes; G, average per cent of change; H, standard error of the mean.

† Standard error of the mean $= \sqrt{\frac{\Sigma d^2}{n(n-1)}}$

action. The fact remains that in normal subjects the *d*-thyroxine has a depressing effect on radioactive iodine uptake of the same order of magnitude as does *l*-thyroxine.

In the few tests that were made with potassium iodide (Table 4) it appears that there may be some effect on uptake of radioactive iodine if the dose used, 2.1 mg. of potassium iodide, contains five times the amount of iodide as that in the effective 0.5 mg. *l*-thyroxine dose. At 10 times this dose, i. e., 4.2 mg. of potassium iodide, there is depression of uptake. It is to be noted that the serum protein-bound iodine

of these subjects was not increased by this medication. We have therefore an effect on uptake by iodide without a rise, and with apparently a slight fall, in circulating protein-bound iodine. These data, however, are insufficient for any conclusion.

In the 13 subjects who were taking a placebo (Table 5) the average difference between the control 24-hour uptake of I^{131} as percent of dummy and the percentage uptake seven days later, with medication, was only 2.40%.

In a number of subjects the entire procedure was performed twice, at an interval ranging from six weeks to one year without treatment (Table 5). The second control was similar to the first for a large proportion of these subjects. There were 21 instances out of the 26 in which the difference in the uptake between the two tests was less than 5%.

The changes in serum protein-bound iodine in each study are important. The average difference between the control and second serum in the normal subjects who were given a placebo capsule was 0.09 γ per 100 cc. The average difference between the two control sera taken from the same person after an interval of two months or more was 0.10 γ per 100 cc. With dosage of 0.5 mg. of sodium *l*-thyroxine once daily by mouth for one week in normal subjects the serum protein-bound iodine increased 1.7 γ per 100 cc., on the average. All subjects showed a change in the direction of increase. Much to our surprise, the same determination under the same dose of sodium *d*-thyroxine showed no significant change; the average difference is 0.10 γ per 100 cc. Whether or not this difference between the isomers is the result of a physiological phenomenon, biochemical error, or statistical illusion is not yet apparent.

The average difference in the control and second serum protein-bound iodine during medication with the ineffective dose of 4 γ of triiodothyronine was 0.2 γ per 100 cc. With the effective doses of 8 and 17 γ of the drug the average difference was 1.1 and 0.7 γ per 100 cc., respectively. In the lower dose material, however, the direction of change was equally divided; in the two lowest effective dose ranges changes occurred in the direction of a lowering of the serum protein-bound iodine in all cases. At dose levels of 35 γ to 140 γ the changes seemed to occur in both directions, varying with the individuals, although the average differences all showed a decrease.

CONCLUSIONS

A study of the effects of sodium *l*-thyroxine (Table 1), triiodothyronine (Table 2), sodium *d*-thyroxine (Table 3), potassium iodide (Table 4), and a placebo (Table 5) has been made on the uptake of radioactive iodine in 144 normal human subjects. No effect of the placebo was found. At least five times as much iodine in inorganic form as in hormonal combination is needed to depress uptake; when this amount is given, the depression occurs without increase in serum protein-bound iodine. Sodium *l*-thyroxine reduces radioactive iodine uptake, with an increase in serum protein-bound iodine; sodium *d*-thyroxine appears to decrease uptake, although the possibility of contamination with the levo isomer must be considered. This effect, if it is real, occurs without increase in serum protein-bound iodine. Triiodothyronine has a maximal effect in reducing uptake at a dose of only 8 γ a day by mouth; 4 γ dosage is ineffective; larger dosage does not seem to be more effective. In this study triiodothyronine seems to be more than five times as potent as thyroxine. There appears to be a fall of serum protein-bound iodine when triiodothyronine produces a reduction of uptake of radioactive iodine.

COMMENT

The dosage response curves seem to indicate three, and possibly four, ways in which these substances act. 1. The iodine affects uptake of the isotope by dilution and by altering the direction of thyroid secretion. 2. The *l*-thyroxine opposes thyroid-stimulating hormone secretion by gradually increasing the level of circulating thyroid hormone. 3. The *d*-thyroxine effects occur similarly, but with less potency, than those of the levo form. 4. Triiodothyronine acts without delay as an intense catalytic metabolic agent in either the central nervous system, pituitary, thyroid, or body tissues. Suppression of uptake results from an immediate reduction of thyroid gland function.

Three important interpretations appear from a study of these responses: First, the *l*-thyroxine has an action itself, which is not due to derived triiodothyronine. If it were otherwise, the effects of the lower dosages of thyroxine would be maximal. If even 10% of the thyroxine were being dehalogenated to triiodothyronine per 24 hours, i. e., 10 γ per day from the 100 γ daily dose of thyroxine, the resulting effect on uptake would be maximal, i. e., 75% instead of 29%. If the thyroxine is effective only after transformation to triiodothyronine, the dehalogenation must be much slower than this. Such a slow rate seems unlikely.

Second, *d*-thyroxine has a biological effect on the pituitary as such; that is, the appearances are not due to contamination with *l*-thyroxine. It seems unlikely that the fed *d*-thyroxine is being transformed to the levo form, since other studies have shown that the fed dextro form is noncalorigenic.[8]

Third, the mode of action of triiodothyronine in reducing uptake of radioactive iodine in these normal young people must be by a different mechanism than that of iodide, sodium *l*-thyroxine, or sodium *d*-thyroxine.

The above considerations indicate that there are two chemical substances, thyroxine and triiodothyronine, each of which has true thyroid hormone activity. This fact, two thyroid hormones, requires a theory of their functions.

We may imagine that thyroid hormone physiology contains two phases, one in which thyroxine acts for caloric homeostasis during benign environmental conditions and another in which triiodothyronine is released from thyroxine to energize the body under acute stress, by a greatly increased rate of catalysis.[9] Thus, a somatic emergency homeostatic mechanism in addition to the pituitary-thyroid axis may be postulated.

When the body is in immediate need of greatly increased hormone action, instead of putting out an enormous mass of thyroxine, it produces the triiodothyronine from the thyroxine already present by an intracellular dehalogenating enzyme. Other

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investigators have demonstrated such an enzyme in thyroid tissue.[10] A disorder of this mechanism might explain thyrotoxic crises in Graves' disease, or Graves' disease itself; that is, the continual unnecessary action of the dehalogenating enzyme, without provocation and without homeostatic inhibition, would keep the body continually under the influence of triiodothyronine.

Since the triiodothyronine is rapidly excreted, immediate replacement of the thyroxine used in the process would require continual replenishment from the thyroid, with a consequent rise of protein-bound iodine and increased uptake of radioactive iodine. The urine in Graves' disease should therefore contain an excess of triiodothyronine. In contrast, patients with simple hyperthyroidism, or that associated with adenomatous goiter, or hyperfunctioning adenoma, which is due to the flooding of the body with thyroxine, should have an excess of this chemical and not of triiodothyronine in the urine.

In conclusion, it seems possible that thyroxine provides calorigenic catalysis for the usual needs of the body in a benign environment. When it accumulates in the circulation, as indicated by rising protein bound iodine, thyroid-stimulating hormone activity is proportionately reduced. A failure of inhibition of this mechanism leads to hyperthyroidism. If an abrupt demand for a 10-fold increase of calorigenic catalytic activity occurs, a dehalogenating enzyme in situ changes the intracellular thyroxine to triiodothyronine, which provides the 10-fold calorigenic activity for a short period of time. A failure of inhibition of this mechanism causes Graves' disease. These speculations suggest several problems for future research.

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Progress in Internal Medicine

PATHOGENESIS OF ESSENTIAL HYPERTENSION

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THE PATHOGENESIS of essential hypertension is still unknown, although progress toward an answer has been made in the past 20 years. According to one view, hypertension is a sign of disease, as are fever and leucocytosis, and "essential" is expressive of our ignorance of its pathogenesis; on this basis, essential hypertension should be regarded as a term comparable to "fever of unknown origin." This view suggests that essential hypertension may be a genus composed of several still undifferentiated species or types of hypertension, which formerly included the hypertensions due to pheochromocytomas, adrenocortical tumors, and renal abnormalities. Another view regards essential hypertension as a definite disease entity with varied manifestations chiefly dependent upon the body areas of localization and degree of progress of the underlying vascular disease process. While this concept is held by a minority of those working in the field, presently available evidence is as supportive of a single basic pathogenetic mechanism as it is of several basic mechanisms. In any event, the term hypertensive vascular disease appears to be preferable to essential hypertension, since the former emphasizes the basic pathophysiologic change rather than one sign of the condition.

As is well known, essential hypertension accounts for 95% of the cases of hypertension seen clinically, the remaining 5% being composed of hypertensions of known, even though incompletely understood, causes. In this group are included the hypertensions of glomerulonephritis, pyelonephritis, renal anomalies, adrenocortical tumors, pheochromocytomas, and coarctation of the aorta. Even in this group, the pathogenesis of only one (pheochromocytoma) is definitely known; viz., an increased secretion of arterenol (norepinephrine) and epinephrine.

The pathogenic relation of malignant hypertension to essential hypertension is also controversial. Most probably malignant hypertension is a greatly accelerated and accentuated form of essential (benign) hypertension, although some authorities regard the two conditions as qualitatively distinct.[1] The same may be said for the typical lesion of essential hypertension, which is arteriolosclerosis, and that of malignant hypertension, which is arteriolonecrosis.

Recent work has confirmed the relation of heredity and body type to the pathogenesis of essential hypertension,[2] but it should be remembered that these factors must operate through pathophysiologic mechanisms, which must be determined. Recent observations have also confirmed the fact that aging and obesity are con-

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1. Smirk, F. H.: Pathogenesis of Essential Hypertension, Brit. M. J. **1**:791, 1949.
2. Thomas, C. B.: The Heritage of Hypertension, Am. J. Sc. **224**:367, 1953.

tributory but not basic factors in the pathogenesis of the condition. There has likewise been recent verification of the older findings that in early, uncomplicated essential hypertension the cardiac output, blood volume, viscosity of the blood, and elasticity of the arteries are within normal limits and that the hypertension is due to increased peripheral resistance in the region of the systemic arterioles. Early the increased resistance results from increased tonus of the smooth muscle of the arterioles, but as the hypertension continues the augmented resistance partly results from progressive arteriolosclerosis, particularly in the kidneys, spleen, pancreas, liver, and brain (in decreasing order). The heart compensates for the augmented resistance by increasing the force of left ventricular contraction in accordance with Starling's law, although if a humoral agent is involved in the pathogenesis of essential hypertension this substance may stimulate cardiac muscle as well as arteriolar smooth muscle. Over a period of time, of course, work hypertrophy of the left ventricle ensues, the basic mechanisms of which are still poorly understood. Capillary and venous pressures are normal in early, uncomplicated essential hypertension, although changes have been reported in the capillary circulation.[3]

NERVOUS SYSTEM

During the past 20 years, research has pointed to neurogenic, endocrine, and renal factors as operative pathogenetically in producing the increased tonus of the arteriolar smooth muscle of early essential hypertension. The neurogenic factor is considered by its proponents to have origin in nervous tension or corticohypothalamic imbalance, as a consequence of which the vasomotor system is periodically, and later continuously, set at a higher level of activity, resulting in increased systemic arteriolar vasoconstriction. The older concept that the increased peripheral resistance of essential hypertension is located primarily in the splanchnic bed has been discarded in favor of that of generalized vasoconstriction. Psychiatrists and others are divided as to whether there is a personality peculiar to essential hypertension. Some psychiatrists maintain that the person with essential hypertension is characterized by repressed aggressiveness, and it has been suggested that appropriate psychologic tests may be capable of predicting the development of essential hypertension, as was previously claimed for the cold pressor test. On the other hand, other phychiatrists believe that the patient with essential hypertension is similar to the normotensive person as far as his psychological and sociological problems and adjustments to them are concerned. Against the concept of continuously increased vasomotor nerve activity is a recent report which denies this for the blood vessels of the forearm and foot in essential hypertension despite the increased peripheral resistance present in these areas.[4] This finding obviously suggests that there may also be increased vasoconstriction elsewhere in the body in the presence of normal vasomotor nerve control. The fact that 5 to 10% of patients with essential hypertension subjected to sympathectomy obtain what is tantamount to a cure suggests, but in no way proves, that this minority may have their hypertension primarily on the basis of increased vasomotor nerve activity. At present the burden of proof

3. Greisman, S. E.: Reactivity of Capillary Bed of Nailfold to Circulating Epinephrine and Nor-Epinephrine in Patient with Normal Blood Pressure and with Essential Hypertension, J. Clin. Invest. **31**:782, 1952.

4. Kowalski, H. J.; Hoobler, S. W.; Malton, S. D., and Lyons, R. H.: Measurement of Vasoconstrictor Tone in the Extremities in Hypertension, Circulation **8**:82, 1953.

is on those who maintain that increased vasomotor nerve tonus is chronically operative in essential hypertension. Certainly there is presently no explanation for this postulated funneling of corticohypothalamic imbalance into vasoconstrictor nerve pathways, any more than there is an explanation for the postulated increased innervation of gastric secretory and motor mechanisms in some patients with peptic ulcer.

The possibility that nervous tension may operate through endocrine changes rather than via the vasomotor system in essential hypertension should be remembered even though there is presently no direct evidence for this concept. Thus hypothalamic-hypophyseal communications could activate the anterior pituitary-adrenal cortex axis and set in motion mechanisms which will be considered below. While there is good evidence that the brain of the dog under certain conditions is capable of acting as an endocrine organ and secreting a humoral pressor agent,[5] there is presently no support for this substance as operative pathogenetically in essential hypertension.

Efforts to reproduce essential hypertension experimentally by alterations of the nervous system have not been too successful. Recent reports have affirmed and denied an older one which stated that in rats selected for emotional instability hypertension develops after repeated strong auditory stimulation with a blast whistle. A minority of dogs subjected to successive ligation of the carotid and vertebral arteries and of subsequently developing collateral vessels in the neck show a degree of hypertension which has not proved sufficiently consistent or pronounced to warrant detailed study. Section of the buffer regulatory (carotid sinus and aortic depressor) nerves of dogs leads to persistent hypertension due to the loss of the normal inhibitory effect of these nerves on the vasomotor (vasoconstrictor) center. This form of experimental hypertension differs in several important respects from essential hypertension—viz., there are increased cardiac output, increased heart rate, increased vasoconstrictor nerve tonus, and absent buffer nerve function—but it should, nevertheless, be subjected to more study than at present.

ANTERIOR PITUITARY-ADRENAL CORTEX AXIS

The possibility that an alteration in the functions of the anterior pituitary-adrenal cortex axis may be pathogenetic in essential hypertension has been entertained for many years, and the now well-documented importance of this axis in water and salt metabolisms has stimulated numerous studies of these metabolisms in essential hypertension. While patients with uncomplicated essential hypertension show normal plasma volume and composition, they demonstrate mild disturbances in sodium chloride and water metabolisms under stress. Thus, the person with essential hypertension retains sodium chloride and water more efficiently than the normotensive person in the face of a sodium-chloride-free diet and shows an increased output of sodium and chloride under load.[6] Moreover, some patients with essential hyper-

5. Taylor, R. D., and Page, I. H.: On the Origin and Properties of a Cerebral Pressor Substance (CPS), Am. J. Physiol. **170**:321, 1952.

6. Birchall, R.; Tuthill, S. W.; Jacobs, W. S.; Trautman, W. J., Jr., and Findley, T.: Renal Excretion of Water, Sodium and Chloride: Comparison of the Responses of Hypertensive Patients with Those of Normal Subjects, Patients with Specific Adrenal or Pituitary Defects, and a Normal Subject Primed with Various Hormones, Circulation **7**:258, 1953.

tension show a significant decrease in blood pressure on a rigidly-adhered-to low-sodium diet of 500 mg. or less per day.

As is well known, large doses of desoxycorticosterone have produced hypertension in normotensive humans. Although there have been conflicting reports concerning the excretion of adrenocortical steroids and their end-products in the urine of patients with essential hypertension, well-documented evidence of a significant difference from normotension is not yet available. Possibly recently developed techniques for the differentiation and quantitation of adrenocortical steroids and degradation products excreted in the urine may reveal a significant increase in a presently unidentified adrenal cortex steroid which may be secreted in small quantity and have a pronounced pressor effect with limited water, electrolyte, and carbohydrate metabolic effects. The recent demonstration that epinephrine, arterenol, and other pressor amines are capable of stimulating the anterior pituitary, and thereby indirectly the adrenal cortex, has suggested the possibility that such a mechanism may operate at an increased level in essential hypertension. So far, however, no one has definitely shown an increase of either corticotropin (ACTH) or the somatotropic hormone in the plasma of patients with essential hypertension. Moreover, epinephrine and arterenol are known to be present in normal amounts, although one group of investigators has reported an increased amount of a pressor amine, pherentasin.[7]

Efforts to reproduce essential hypertension in animals by alterations in electrolyte metabolism and in endocrine balance have not been too successful. Large doses of desoxycorticosterone administered parenterally, particularly with sodium chloride orally, produce hypertension in the rat. However, results in the dog have been less consistent. Increased tissue fluid and blood volume resulting from the retention of sodium chloride are probably not the principal cause of this experimental hypertension, although a high-salt diet alone in rats, but not in dogs, will produce some degree of hypertension. In general, it is easier to produce hypertension in the rat than in the dog. There is also ample evidence that a few injections of certain crude and semipurified anterior pituitary extracts, including growth hormone preparations, will produce hypertension in rats. Findings in the dog have been less consistent. In the present state of our knowledge, these experimental hypertensions bear more similarity to the hypertension seen clinically in pituitary basophilism and in adrenocortical tumors than they do to essential hypertension.

KIDNEY

The possibility that changes in renal function may play a pathogenetic role in essential hypertension has been suggested and denied for many years. To my knowledge, the only direct findings linking the kidney to the pathogenesis of essential hypertension are an increased concentration of vasoexcitatory material[8] (VEM) (produced by the kidney) and angiotonin (hypertensin)[9] in the plasma, the aerobic

7. Davies, D. F.; Olsen, N. S., and Schroeder, H. A.: Pressor Substances in Arterial Hypertension: IV. Quantitative and Qualitative Studies of Pherentasin, Circulation **5**:380, 1952.

8. Shorr, E.: The Participation of Hepatorenal Factors in Experimental Renal Hypertension: Hypertension, A symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 92.

9. Kahn, J. R.; Skeggs, L. T., Jr.; Shumway, N. P., and Wisenbaugh, P. E.: The Assay of Hypertensin from the Arterial Blood of Normotensive and Hypertensive Human Beings, J. Exper. Med. **95**:523, 1952.

formation of VEM by the kidney in vitro, and an altered histochemical pattern in the kidney in essential hypertension.[8] All other evidence for the renal origin of essential hypertension is indirect and frequently by analogy. Thus semipurified hog renin or angiotonin administered intravenously to experimental animals and angiotonin administered intravenously to man have been shown to produce changes simulating the hemodynamic changes of essential hypertension (renin, of course, is the proteolytic enzyme produced by the tubule cells of the renal cortex which acts on renin substrate [hypertensinogen], an alpha-2-globulin of the plasma, to form the polypeptide, angiotonin, which has a stimulating effect on the smooth muscle of the arterioles). Furthermore, there are many similarities and no important differences between experimental renal hypertension produced by partial constriction of the renal arteries in dogs and other species and early essential hypertension in man, except the obvious and compelling difference of constricting silver clamps. Similarity obviously does not necessarily mean even a partial common pathogenesis.

Unfortunately, the pathogenesis of experimental renal hypertension produced by renal artery constriction (or by compression of the kidney by a perinephric membrane or a figure-of-eight ligature) has not yet been determined with certainty. The three principal hypotheses are alteration in the renin-angiotonin mechanism, decreased secretion of a renal blood pressure regulating hormone, and increased formation of pressor amines by the kidney. Evidence for the renin hypothesis includes the prevention and successful treatment of experimental renal hypertension in dogs with semipurified hog renin. Since hog renin is a foreign protein, it produces an antisubstance or antibody (antirenin), which neutralizes the pressor effect not only of hog renin but also of dog renin. However, semipurified hog renin contains others vasoactive proteins, including so-called sustained pressor substance, (SPS), and the antihypertensive effect may possibly be due to antibodies to these. In any event, the antihypertensive effects are well correlated with the antirenin titers.[10] A pathogenetic role for renin in experimental renal hypertension is further suggested by the finding that the passive transfer of high titer antiserum from one dog to another is similarly effective antihypertensively.[11] Moreover, renin and hypertensin have been suggested to be present in increased concentration in the plasma of dogs with chronic renal hypertension.[12]

Perhaps more important as evidence that the kidney and renin may play a role in the pathogenesis of essential hypertension is the finding that hog renin therapy is successful in so-called spontaneous hypertension in the dog.[13] Laboratory studies have revealed no changes from the normal in these dogs, except an increase in peripheral resistance, an increase in systolic and diastolic blood pressures, and an increase in the concentration of plasma VEM and VDM, which are also the only

10. Wakerlin, G. E.; Bird, R. B.; Brennan, B. B.; Frank, M. H.; Kremen, S.; Kuperman, I., and Skom, J. H.: Treatment and Prophylaxis of Experimental Renal Hypertension with "Renin," J. Lab. & Clin. Med. **41**:708, 1953.

11. Kuperman, I., and Wakerlin, G. E.: Treatment of Experimental Renal Hypertension in Dogs with Antirenin, Fed. Proc. **12**:80, 1953.

12. Skeggs, L. T.; Kahn, J. R., and Shumway, N. P.: The Isolation of Hypertensin from the Circulating Blood of Normal Dogs with Experimental Renal Hypertension by Dialysis in an Artificial Kidney, Circulation **3**:384, 1951.

13. Katz, J.; Skom, J. H., and Wakerlin, G. E.: Treatment of Spontaneous Hypertension in Dogs with Semipurified Hog Renin, Program of the 26th Scientific Sessions of the American Heart Association, Atlantic City, April 9-12, 1953, p. 70.

findings in early essential hypertension in man. Since spontaneous hypertension in the dog may represent the same condition as essential hypertension in man, the former is deserving of more study.

Trial of semipurified hog renin in the therapy of essential hypertension is suggested by these findings. Unfortunately, however, antirenin to hog renin produced in man does not neutralize human renin, and a course of semipurified hog renin in hypertensive humans has been shown to be without antihypertensive effect.[14] However, the demonstrated effectiveness of passive immunization with antiserum containing antirenin in experimental renal hypertension in the dog suggests a heretofore unavailable method for studying the possible role of the kidney and renin in the pathogenesis of essential hypertension. Since antirenin to human renin produced in the rabbit, dog, and goat neutralizes human renin, our research group is presently collecting purified antirenin to human renin from these species to study the effect of passive immunization of patients with essential hypertension. If significant antihypertensive effects are obtained, a pathogenetic role for the kidney and renin would be suggested. Before such a study can be made, however, important animal studies to demonstrate the safety of the procedure must be completed. Should an appreciable percentage of patients with essential hypertension prove to have hypertension primarily or dominantly on a renal basis involving renin, various research groups would be stimulated to join those presently attempting to alter the antigenicity of hog renin to overcome the species difference which now precludes the possible successful use of renin in the treatment of human hypertension.

In this consideration of the role of the kidney and renin in essential hypertension, comment should be made on the often-cited finding that there is no significant difference between the plasma renin concentrations of humans with essential hypertension and normotensive humans. This should not be used as a conclusive argument against the renin hypothesis, since present methods for the assay of renin may not be sufficiently specific and sensitive to detect differences in renin concentration which have recently been shown to exert a chronic pressor effect in experimental animals.[15] Furthermore, no one has demonstrated a significant difference between the insulin concentration of the plasmas of normal persons and those of patients with hyperinsulinism and yet insulin is certainly conceded to be related pathogenetically to the latter.

The possibility that the kidney may play a pathogenetic role in essential hypertension is strengthened by the demonstration that excessive constriction of the renal arteries in animals produces experimental malignant hypertension which resembles clinical malignant hypertension. Recent work on the prophylaxis of experimental malignant hypertension in the dog with hog renal extracts containing renin suggests that the hypertension is due to renin and that the necrotizing arterial and arteriolar lesions, uremia, and death are associated with the nonrenin fraction of renal cortex.[16]

14. Goldblatt, H.; Haas, E., and Lanfrom, H.: Antirenin in Man and Animals, Trans. A Am. Physicians **64**:122, 1951. Helmer, O. M.; Shipley, R. E.; Pierce, J. D., and Kohlstaedt, K.: Antibodies Against Renin and "Sustained Pressor Principle" Produced by Injections of Kidney Extracts, abstracted. J. Lab. & Clin. Med. **33**:1484, 1948.

15. Blacket, R. B.; Deporter, A.; Pickering, G. W.; Sellers, A. L., and Wilson, G. M.: Hypertension Produced in the Rabbit by Long Continued Infusions of Renin, Clin. Sc. **9**:223, 1950.

16. Burns, R. O., and Wakerlin, G. E.: Protection Against Hypertension, Arteriolonecrosis, and Death by Hog Renal Extracts in Experimental Malignant Hypertension, Circulation Res., to be published.

In these experiments some dogs were protected not only against the blood pressure increase of experimental malignant hypertension but, more importantly, against arterial and arteriolar necrosis, uremia, and death. Such findings offer hope that the pathogenesis of clinical malignant hypertension will one day be determined and its more effective therapy follow. The possibility that the kidney may play a role in the pathogenesis of clinical malignant hypertension is further suggested by recent observations that the pathologic and clinical signs of malignant hypertension can also be produced by bilateral nephrectomy in dogs, with prolonged survival obtained by peritoneal lavage.[17]

GENERAL CONSIDERATIONS

Obviously much work remains to be done before the pathogenesis of essential hypertension is determined. Neurogenic, endocrine, and renal factors must be further explored and other avenues investigated. The possibility of a basic change in the metabolism of vascular smooth muscle and cardiac muscle in essential hypertension should be studied. The normality of pulmonary blood pressures in uncomplicated essential hypertension has too readily been explained on the basis of the sparse smooth muscle of the pulmonary arterioles. The possibility of a change in the carotid sinus mechanisms, as recently proposed by Volhard and his colleagues, is deserving of more attention.[18] Long term sociologic and epidemiologic studies may yield important information.[19]

On the basis of evidence obtained chiefly during the past 20 years, the following working hypothesis for the pathogenesis of essential hypertension, somewhat resembling but more specific than others recently offered,[20] is proposed. Episodes of stress and corticohypothalamic imbalance activate a chain of pathophysiologic events which at first is intermittent but which eventually becomes continuous. An increased secretion of renin and other renal vasoactive substances results from renal hemodynamic changes produced by increased neurogenic renal vasoconstriction and possibly from the increased innervation of long-postulated secretory nerve fibers to the tubule cells of the renal cortex. Simultaneously there may be a decreased secretion of a renal blood-pressure-regulating hormone antagonistic to renin. In addition to exerting a pressor effect via angiotonin formation, renin stimulates the anterior pituitary to produce an increased secretion of adrenocorticotropin [21] and possibly somatotrophin, which stimulate the adrenal cortex to secrete more steroids, one of which has a pronounced pressor effect and minimal effects on carbohydrate and salt metabolisms. This steroid also acts on the kidney to increase the secretion of renin and other renal pressor substances. After a number of episodes of activation, this

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18. Kezdi, P.: Sinoaortic Regulatory System: Role in Pathogenesis of Essential Malignant Hypertension, A. M. A. Arch. Int. Med. **91**:26, 1953.

19. A Symposium on Essential Hypertension: An Epidemiologic Approach, Commonwealth of Massachusetts, Boston, Wright & Potter Printing Co., 1951.

20. Page, I. H.: The Renin-Angiotonin Pressor System, Hypertension, A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 66. Braun-Menendez, E.: Experimental Hypertension, Hypertension, A Symposium, edited by E. T. Bell, Minneapolis, University of Minnesota Press, 1951, p. 177.

21. Sevy, R. W., and Wakerlin, G. E.: Endocrine Factors in Experimental Renal Hypertension, Am. J. Physiol. **172**:129, 1953.

mechanism becomes self-sustaining as a result of an alteration in the metabolism of the renal tubule cells responsible for the secretion of renin and other vasoactive substances.

Obviously there are other interactions which probably play a role in this complex mechanism. Thus, in addition to forming angiotonin and acting on the anterior pituitary, renin may directly stimulate the adrenal cortex. VEM is known to sensitize the smooth muscle of the precapillaries to the constricting effect of epinephrine and arterenol, and epinephrine has been reported to sensitize blood vessels to the constricting effect of hypertensin. Episodes of stress and corticohypothalamic imbalance through hypothalamic-hypophyseal communications will, of course, more directly stimulate the anterior pituitary to an increased secretion of hormones activating the adrenal cortex. Renin and corticohypothalamic imbalance may also stimulate the secretion of an anterior pituitary renotrophic hormone.

In additions to interrelations among the nervous system, the kidney, the endocrines, and the musculature of the arterioles and the heart, this hypothesis postulates a potential basic metabolic difference (certainly quantitative and possibly qualitative) between the renal tubule cells of persons with essential hypertension and normotensive persons, just as there is a poorly understood difference between the beta cells of the islets of Langerhans of diabetic and nondiabetic persons. The hypothesis suggests that specific treatments may be devised to interrupt the proposed vicious circle at more than one point. This has already been shown to be true for experimental renal hypertension in the dog, which has been successfully treated with antirenin to hog renin,[10] with repeated courses of crude anterior pituitary extract,[21] and, curiously enough, with the pressor amine, hydroxyamphetamine (Paredrine).[22] The hypothesis regards essential hypertension as a single clinical entity, with opportunity for various degrees of functional and later anatomical change in different tissues, organs, and systems. While the hypothesis is supported by studies on experimental hypertensions, some of which have been mentioned above, its documentation by observations on essential hypertension is presently meager. In any event the numerous interrelations suggested by the hypothesis would account for the slow progress of research in the field.

SUMMARY

The pathogenesis of essential hypertension is presently unknown, although there have been advances in knowledge during the past 20 years, particularly from studies of experimental hypertensions. A working hypothesis largely based on such studies is presented. Obviously more work must be done before the pathogenesis of essential hypertension is understood and specific therapy devised.

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Case Reports

RUPTURE OF AORTIC ANEURYSM INTO SUPERIOR VENA CAVA

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SYPHILITIC aortic aneurysms may pursue a variety of courses and, although the condition is uncommon, rupture of an aortic aneurysm into the superior vena cava produces a quite dramatic clinical picture.

Hunter [1] in 1757 discussed aortic aneurysms in the chest and arteriovenous aneurysms in the arm, but the first case of an aortic aneurysm rupturing into the superior vena cava was reported in 1833.[2] A review of the literature from 1833 to the present time has disclosed a total of 117 cases.[3] Three authors [4] have presented excellent statistical analyses of the clinical and pathologic features. These reviews reveal that rupture of an aortic aneurysm into the superior vena cava usually occurs in males during the fourth or fifth decades. Symptoms begin with the sudden onset of a moderate to severe superior vena cava obstruction syndrome. Physical examination presents the striking appearance of moderately severe edema, venous distention, and cyanosis sharply limited to the head, neck, arms, and upper chest, in a dyspneic seriously ill patient. Although the aortic valve is almost always intact and competent, peripheral signs of aortic insufficiency are often present, due to rapid dissipation of the arterial

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2. Beevor: Case Reported Before the Middlesex Medical Society, Lancet **1**:800, 1832-1833; Interesting Pathological Facts, ibid. **2**:63, 1832-1833.

3. (*a*) Pepper, W., and Griffith, J. P.: Varicose Aneurysms of the Aorta and Superior Vena Cava, Am. J. M. Sc. **100**:329, 1890. (*b*) Woolley, P. G.: A Series of Ruptured Aortic Aneurysms, Am. J. Syph. **1**:426, 1917. (*c*) Shennan, T.: Spontaneous Arteriovenous Aneurysm in the Thorax, Edinburgh M. J. **32**:325; **32**:410, 1925. (*d*) House, S. J., and Goodpasture, E. W.: Spontaneous Arteriovenous Aneurysm in the Thorax, Am. Heart J. **3**:682, 1928. (*e*) Armstrong, E. L.; Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax: Review of the Literature; With a Report of 2 Cases, Arch. Int. Med. **63**:298, 1939. (*f*) Hussey, H. H.; Katz, S., and Yater, W. M.: The Superior Vena Caval Syndrome: Report of 35 Cases, Am. Heart J. **31**:1, 1946. (*g*) Wunderman, D. C.: A Report of a Case of Aortic Aneurysm Rupturing into the Superior Vena Cava, South. M. J. **39**:813, 1946. (*h*) Murnaghan, D. P.: Rupture of an Aortic Aneurysm into the Superior Vena Cava with Obstruction, Canad. M. A. J. **59**:370, 1948. (*i*) Danaraj, T. J.: A Case of Arteriovenous Aneurysm, Brit. M. J. **1**:1124, 1949. (*j*) Alex, M.: Rupture of an Aortic Aneurysm into the Superior Vena Cava, Am. Heart J. **39**:455, 1950. (*k*) Sirota, J. H.: Spontaneous Perforation of an Aortic Aneurysm into the Superior Vena Cava with Survival for 136 Days, ibid. **39**:782, 1950. (*l*) Clinical Pathological Conference: Superior Vena Caval Obstruction from a Ruptured Aneurysm, J. Kansas M. Soc. **52**:20, 1951. (*m*) Marchand, E. J.; Heitmancik, M. R., and Herrmann, G. R.: Extracardiac Arteriovenous Fistulas in the Thorax, Am. Heart J. **42**:682, 1951. (*n*) Beevor.[2]

4. Footnote 3*c*, *e*, and *j*.

blood pressure into the superior vena cava. A murmur, usually the characteristic continuous machinery type of an arteriovenous shunt, is heard over the aneurysm, and a thrill may be associated with systole. Contrary to what might be anticipated, pulsation of the congested neck veins is reported to have occurred in only about 10% of the cases. Laboratory findings commonly disclose a positive serologic test for syphilis, a marked elevation of upper extremity venous pressure, and a prolonged arm to tongue circulation time. Oxygen saturation studies by cardiac catheterization [3h] or comparison of peripheral blood values [3m] provide clinching evidence. Roentgenographic studies reveal the pulsating shadow of the saccular aneurysm. The clinical course after the rupture has occurred is usually steadily downhill, ending in death. However, a few patients have lived for several months and three are reported to have survived,[3e] apparently on the basis of collateral circulation development. No specific therapy alters the course of the disease. One attempt at surgery [3k] was unsuccessful, but perhaps future development in surgical techniques may make this approach feasible in some cases. The pathologic finding is syphilitic aortitis with a saccular aneurysm of varying size and position in the ascending aorta and one or more perforations of different size and location of the aneurysm into the superior vena cava.

REPORT OF A CASE

History.—A 56-year-old white married male house painter entered the Veterans Administration Hospital, Portland, Ore., on Jan. 19, 1952, complaining of swelling of the neck and face, dyspnea, cough, chest and abdominal pain, dizziness, and low back pain. He stated that an abnormality was first noted on a chest x-ray made during his separation from the army in 1919, but he was then asymptomatic and no further study was done. He had no symptoms until 1937, when mild precordial chest pain, associated with exertion, developed. This pain persisted, and in 1949 he first noted a spontaneous intermittent mild upper abdominal pain, which was not related to meals. He then sought medical care, and he was told that a chest x-ray, taken in November 1949, revealed a tumor. However, no further investigation was made. He continued to work, but symptoms persisted, and he again consulted a physician, in April 1951. A verbal report to me from that physician related to the finding of an upper anterior mediastinal mass corresponding to, but slightly larger than, the "tumor" seen on the roentgenogram in November 1949. Fluoroscopy failed to disclose pulsation, and the mass was thought to be separate from the heart and great vessels. The right diaphragm was somewhat elevated, and its motions were reduced. The heart was normal, and no murmurs were present. The blood pressure was 112/60. A serologic test for syphilis was not done. A cholecystogram revealed cholelithiasis. Because of the possibility of a mediastinal tumor, a thoracic surgeon advised an exploratory thoracotomy, which the patient refused. He then sought care from a naturopathist-chiropractor, who prescribed a diet and oral medication, with some symptomatic improvement. However, in November 1951, a mild but persistent slightly productive cough developed. A few episodes of mild vertigo were noted in December 1951. About the middle of December 1951, a cold developed and the patient was treated by a druggist, with improvement. He continued to work until the morning of Jan. 13, 1952, when he awoke with marked face and neck swelling, mild dyspnea, and moderately severe substernal pain. The pain subsided in three days, but the dyspnea persisted and the facial edema progressed, with extension of edema into both arms. The patient again sought medical care and was admitted to this hospital on Jan. 19, 1952.

The past history revealed that he had gonorrhea in 1919 and again in about 1922, at which time he believed that he also had a penile lesion. Although he was not told that he had syphilis, he had a long course of injections given by a specialist, which he thought was for gonorrhea. He never knew of a positive serologic test for syphilis.

Physical Examination.—Physical examination revealed a well-developed moderately well-nourished alert cooperative adult white male, breathing quietly while at rest in bed. He appeared chronically ill and presented an obvious moderately severe edema of the head, neck, arms, and upper chest, with marked distention of the superficial veins and mild cyanosis of the edematous

areas. The blood pressure in the right arm was 130/50 to 0; in the left arm it was 118/60 to 20. The pulse rate was 100, and the temperature was 98.8 F. Funduscopic examination of the eyes showed only minimal tortuosity of the vessels; there was no papilledema, hemorrhage, exudate, or definite venous congestion. Except for the moderate edema, cyanosis, and marked venous

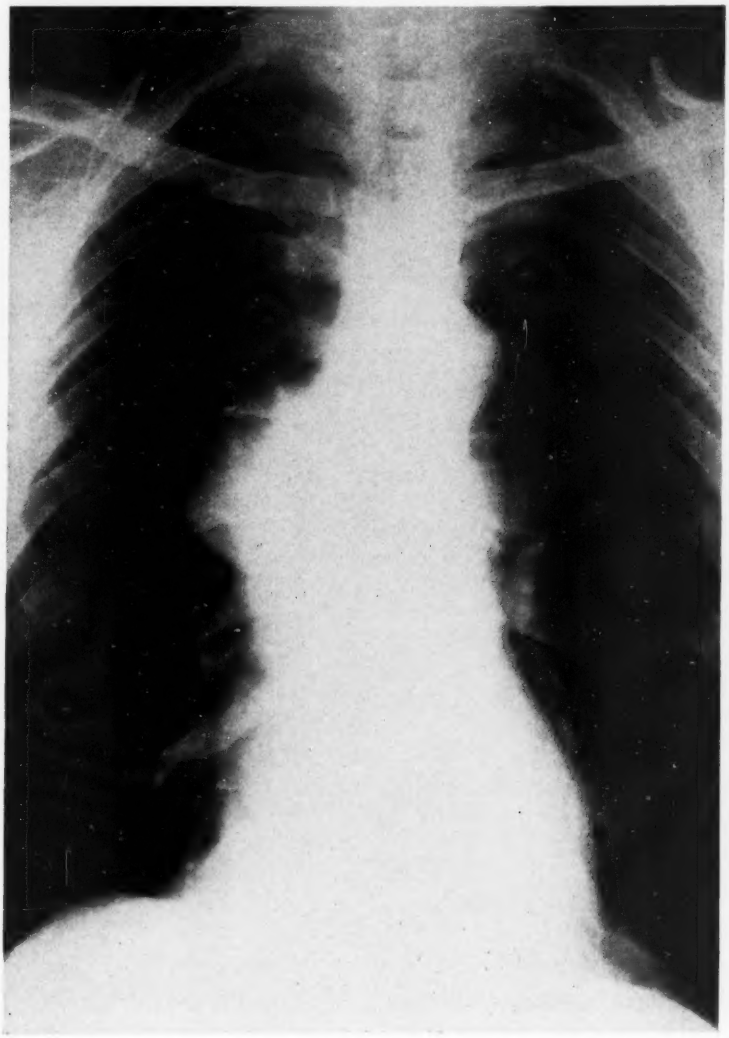

Fig. 1.—X-ray of the chest taken Nov. 10, 1949, which reveals the right hilar shadow which subsequently proved to be the aortic aneurysm.

distention, the remainder of the findings of the head and neck were within normal limits. The chest was symmetrical, and expansion was equal. The trachea was deviated slightly to the left. Both lungs were resonant throughout, except for a rounded area of dullness extending about 6.0 cm. out from the mediastinum under the right third anterior rib and moderate elevation of

the right diaphragm. Breath sounds were normal, and no rales were heard. The left heart border was at the midclavicular line, and the rhythm was regular. Mitral area sounds were clear, with a Grade II systolic murmur. Tricuspic and pulmonic area sounds were regular, but analysis was obscured by a very loud continuous machinery murmur with a marked systolic

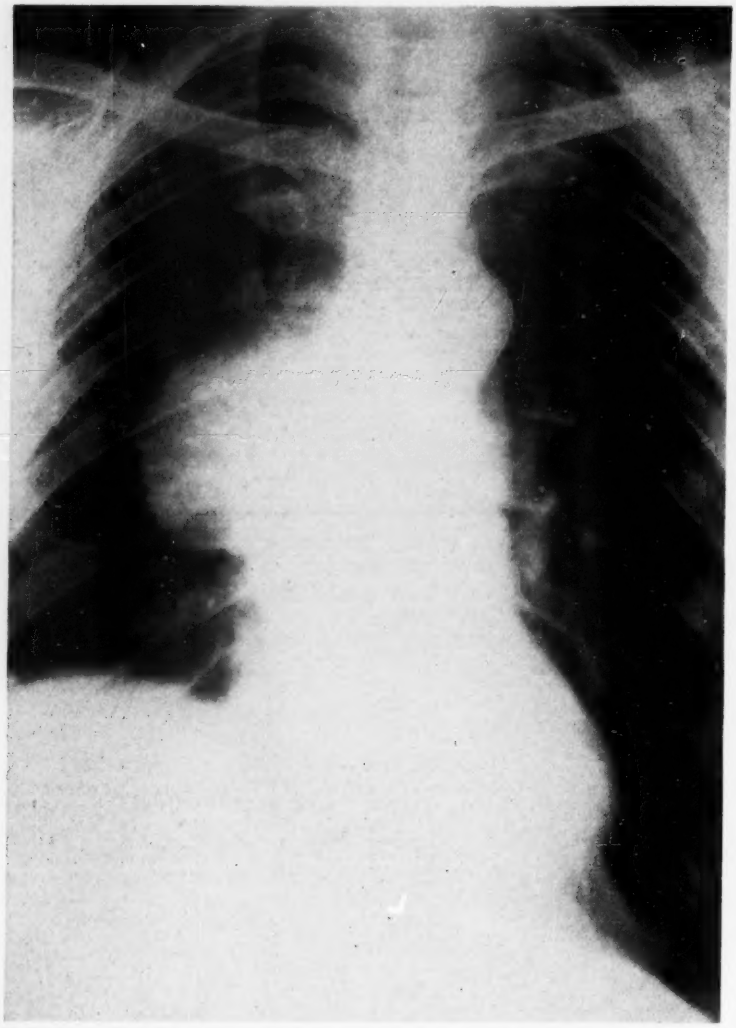

Fig. 2.—X-ray of the chest, April 18, 1951, showing an increase in the size of the aneurysm and the development of right diaphragmatic elevation.

accentuation that centered over the right second and third anterior ribs and extended into the neck and axilla and over the entire precordium. The aortic valve sounds were not heard. A thrill synchronous with systole was easily palpable in the right supraclavicular fossa and over the anterior ends of the right second and third ribs. Sounds from the radial arteries presented a pistol shot character. The femoral and dorsalis pedis pulsations were strong. A systolic

murmur was heard over the femoral arteries. There were no visible pulsations in the distended neck veins. No masses or viscera were palpable in the abdomen. There was no venous distention or edema below the upper third of the chest wall. The remainder of a complete physical examination was within normal limits.

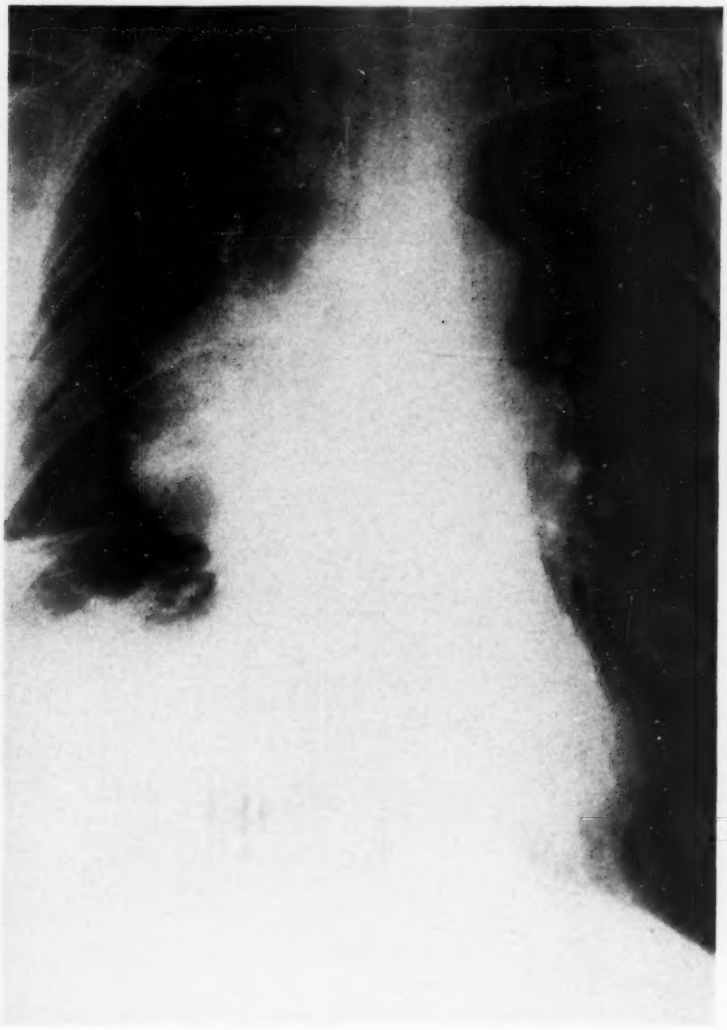

Fig. 3.—X-ray of the chest, posteroanterior view, Jan. 21, 1952, showing a further increase in the size of the aneurysm and in the right diaphragmatic elevation.

Laboratory Studies.—Results of urinalysis were essentially normal. The red blood cell count was 4,300,000, with 11.5 gm. of hemoglobin, and the white blood cell count was 20,400, with 86% neutrophiles, 3% staff cells, and 11% lymphocytes. The standard Kahn test was reported as 4+, 3+, 2+, and the quantitative Kahn test was 4+, 4+, 4+, 4+, 3+ (120 Kahn units). The complement-fixation and cardiolipin tests were both 4+. The blood urea nitrogen was

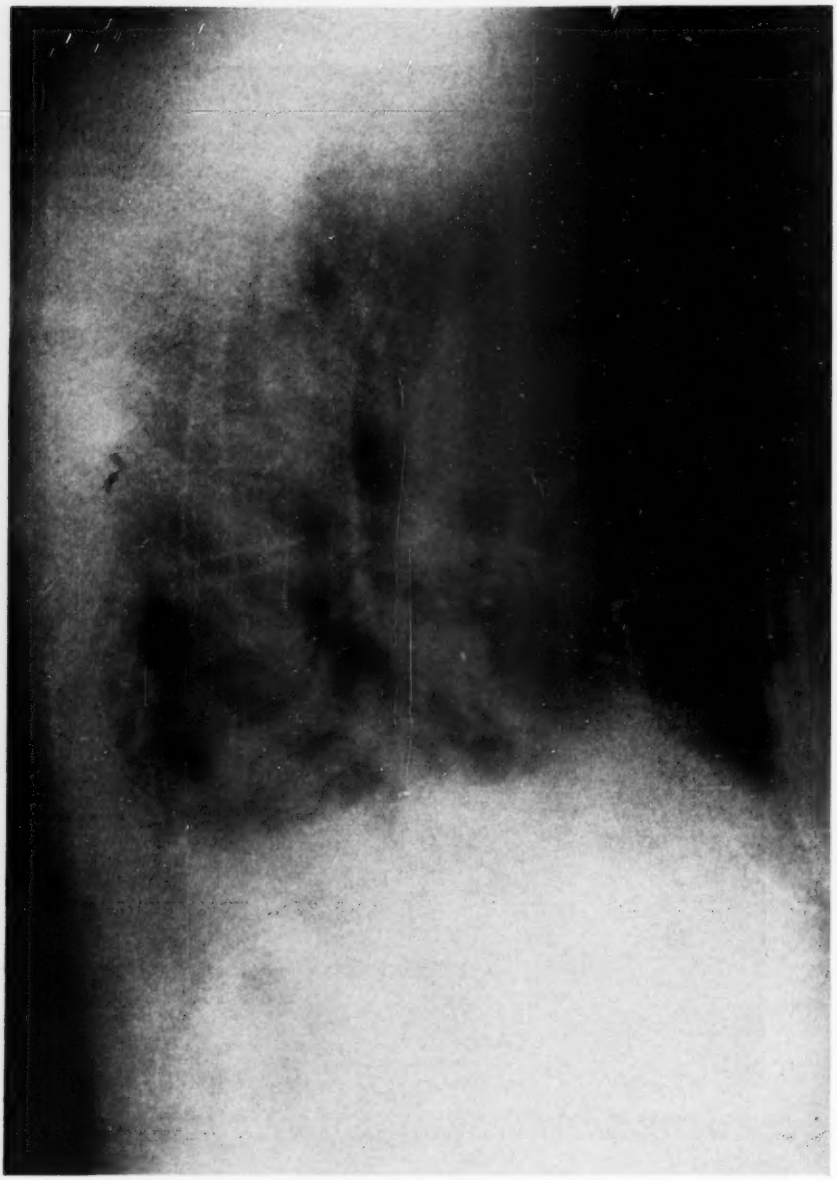

Fig. 4.—X-ray of the chest, lateral view, Jan. 21, 1952.

42.7 mg. per 100 ml. A spinal puncture with the patient in the horizontal position revealed an initial pressure of 430 mm. of water and a final pressure of 380 mm., apparently a reflection of the elevated venous pressure. Analysis of the spinal fluid, including the complement-fixation test, showed no abnormalities. An electrocardiogram was interpreted as showing left ventricular preponderance and generalized myocardial ischemia. Venous pressure in the right antecubital fossa was 41.2 cm. of water, with an arm to tongue (dehydrochloric acid [Decholin]) time of 57 seconds and an arm to lung (ether) time of 30 seconds.

Roentgenographic Studies.—Posteroanterior, lateral, and oblique views of the chest revealed a large rounded fairly sharply circumscribed mass bulging into the right lung field from the right

Fig. 5.—The heart and aorta at autopsy, with the aneurysm opened and a probe in the perforation.

hilum. It was of soft tissue density and contained no calcifications. The mass could not be separated from the ascending aorta and extended anteriorly to the sternum. A rather pronounced elevation of the right hemidiaphragm was noted. The left lung was clear, and there was no erosion of the sternum or ribs. Comparison with films taken elsewhere, in November 1949 and in April 1951, disclosed steady progression of the size of the mass and development of elevation of the right hemidiaphragm. Fluoroscopy of the chest showed definite expansile pulsation of the mass and very minimal motion of the elevated right hemidiaphragm.

Clinical Course.—The patient had been digitalized before admission; consequently this therapy was continued. During hospitalization he became steadily more incapacitated by exertional

dyspnea, orthopnea, and weakness. The edema about the face and neck remained unchanged but that in both arms became worse. Syphilitic therapy was instituted on Jan. 25, with 1.5 cc. of bismuth subsalicylate in oil, intramuscularly, and then was repeated every four days for a total of four doses, the course being completed on Feb. 6. Edema of the penis was first noted on Feb. 5, and this rapidly extended in 24 hours to include the scrotum and legs. A salt-free diet was then started, and an injection of a mercurial diuretic was given. An intensive course of penicillin therapy was proposed but was not given because of the patient's quiet death at 5:05 a. m. on Feb. 7, just 25 days after the onset of the face and arm edema. During the final 10 days of life he was bedfast and required occasional injections of meperidine (Demerol) for comfort.

Fig. 6.—View of the perforation from the vena cava side.

Clinical Diagnoses.—These were (1) aneurysm, saccular, of the ascending aorta, due to syphilis, with partial obstruction of the superior vena cava; (2) rupture of the syphilitic aortic aneurysm into the superior vena cava; (3) syphilitic valvulitis, aortic valve, with insufficiency.

Postmortem Examination.—The significant autopsy findings were confined to the chest. When the breast plate was removed, a large saccular aneurysm of the ascending aorta was immediately apparent. It started just above the aortic valve and extended 11 cm., to include the entire ascending aorta. The maximum circumference was 20 cm. When it was opened the intima was tree-bark-like and marked atherosclerotic changes were seen. At the base of the aneurysm along the right lateral wall was a round sharply circumscribed area, 5 cm. in diameter, of further dilation,

which was very thin and intimately adherent to the surface of the upper lobe of the right lung; this contained a small mural thrombus. At the upper right lateral margin of the aneurysm there was a slit-like defect, 1 cm. in diameter, passing from the lumen of the aneurysm into the lumen of the immediately adjacent superior vena cava, which was stretched over the lateral and posterior surface of the aneurysm. This perforation was 4 cm. above the entrance of the azygos vein into the superior vena cava. The heart weighed 405 gm., and its maximum transverse diameter was 13 cm. The left ventricle was 1.5 cm. thick, and the right ventricle 0.5 cm. The coronary arteries revealed minimal atherosclerotic thickening but were patent throughout. All valves were normal except the aortic valve, which showed slight separation at the commissures and some calcification of the leaflets. Both pleural cavities contained approximately 1500 ml. of thin yellow fluid. Each lung weighed 650 gm. The middle and lower lobes of the right lung and part of the lower lobe of the left lung were atelectatic. A bulging area, 5 cm. in diameter, adjacent and adherent to the aortic aneurysm, was present on the medial aspect of the base of the upper lobe of the right lung. The remainder of the gross findings, including those of the brain and spinal cord, were not remarkable.

Microscopic examination of the aorta revealed a far advanced atherosclerotic process. In addition, the adventitia was markedly thickened and extensively infiltrated with lymphocytes and plasma cells. Most of this infiltration was perivascular, and there was considerable thickening of the arterioles in the adventitia. The media in most sections was almost completely destroyed. There was a slight amount of calcareous material in scattered areas. On several sections the aorta was adherent to lung tissue.

Pathologic Diagnosis.—The diagnosis was syphilitic aortic aneurysm with arteriovenous fistula connecting the aneurysm with the superior vena cava.

SUMMARY

A review of the literature disclosed 117 previous cases of rupture of an aortic aneurysm into the superior vena cava. The usual clinical appearance and findings as obtained from these reports are presented, and an additional case is reported.

PHEOCHROMOCYTOMA BEFORE AND AFTER SURGERY

Report of a Case with Pharmacologic Tests, Roentgenologic Diagnosis, and Endocrine Survey

EUGENE B. LEVIN, M.D.
SAN FRANCISCO

ALTHOUGH many excellent articles [1] continue to review the literature of cases of paroxysmal hypertension produced by adrenal medulla tumors, little has been mentioned about the various endocrine manifestations of this condition. This paper, in addition to discussing the pharmacologic and roentgenographic means of diagnosis, will specifically emphasize the various endocrine findings and their significance.

Selye [2] first called attention to the effects of stress on the adrenal-pituitary axis. Further work pointed to a specific relationship between epinephrine and this axis. Experimentation with epinephrine administration in animals and later in man resulted in a decrease in the circulating eosinophiles, decrease in adrenal ascorbic acid and cholesterol levels, and an increase in 17-ketosteroid excretion in the urine.[3] From these findings a test has been devised using subcutaneous injection of epinephrine to ascertain the integrity of this system.[3a] In cases of pheochromocytoma, in which epinephrine and arterenol (norepinephrine) have been found intermittently or constantly elevated in the blood stream, one is interested in the effects of these agents on the adrenal pituitary axis.

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1. (*a*) Wilkins, R. W.; Greer, W. E. R.; Culbertson, J. W.; Halperin, M. H.; Litter, J.; Burnett, C. H., and Smithwick, R. H.: Extensive Laboratory Studies of a Patient with Pheochromocytoma Before and After Successful Operation, with a Note on the Trial of Piperidylmethyl Benzodioxane to Differentiate Such Conditions from Essential Hypertensive Vascular Disease, Arch. Int. Med. **86**:51, 1950. (*b*) Grahams, J. B.: Pheochromocytoma and Hypertension: Collective Review, Surg., Gynec. & Obst. **92**:105, 1947. (*c*) Aranow, H.: Pheochromocytoma, in Monographism Medicine, Baltimore, Williams & Wilkins Company, 1952, p. 179. (*d*) Aranow, H., Jr.: Symposium on Cardiovascular Diseases: The Differential Diagnosis of Pheochromocytoma, M. Clin. North America **34**:757, 1950. (*e*) Bartels, E. C., and Cattell, R. B.: Pheochromocytoma: Its Diagnosis and Treatment, Ann. Surg. **132**:903, 1950. (*f*) Calkins, E.; Dana, G. W., and Howard, J. E.: Current Methods of Diagnosis of Pheochromocytoma, J. A. M. A. **145**:880, 1951. (*g*) Shapiro, A. P.; Baker, H. M.; Hoffman, M. S., and Ferris, E. B.: Pharmacologic and Physiologic Studies of a Case of Pheochromocytoma, Am. J. Med. **10**:115, 1950.

2. Selye, H.: The General Adaptation Syndrome and Diseases of Adaptation, J. Clin. Endocrinol. **6**:117, 1946.

3. (*a*) Recant, L.; Hume, D. M.; Forsham, P. H., and Thorn, G. W.: Studies on the Effect of Epinephrine on Pituitary-Adrenocortical System, J. Clin. Endocrinol. **10**:187, 1950. (*b*) Long, C. N. H.: The Conditions Associated with the Secretion of the Adrenal Cortex, Federation Proc. **6**:461, 1947. (*c*) Corcoran, A. C., and Page, I. H.: Methods for the Chemical Determination of Corticosteroids in Urine and Plasma, J. Lab. & Clin. Med. **33**:1326, 1948. (*d*) Sayers, G.: Regulation of the Secretory Activity of the Adrenal Cortex, Am. J. Med. **10**:539, 1951.

The clinical manifestations which result from these excessive hormonal secretions are such that often the patient is thought to be suffering from a disease of hypermetabolism. The initial diagnosis of diabetes mellitus is made frequently.[4] Less frequently, patients have thyroidectomies[5] and treatment with thiouracil[5b] and strong iodine solution, U. S. P. Lugol's solution,[4b] for thyrotoxicosis. Rarely, specific attention is given to sexual changes, particularly impotence.[6]

A study of this case and a selective review of the literature may help clarify some of the endocrine aspects of pheochromocytoma.

REPORT OF CASE

J. J., a 33-year-old white man, entered the hospital complaining of recurrent attacks of profuse sweating, nervousness, tremor of the hands, headaches, and a tight sensation in the chest during the past three to four years. Eight years before admission he was first told that he had high blood pressure. The blood pressure varied considerably and at times was normal. Three years ago, a psychiatric treatment had included weekly subcutaneous injections of histamine, which reproduced the above symptoms and made the patient quite ill for short periods of time after the injection. For the past two years, another physician had treated him with biweekly injections of testosterone and daily sublingual administration of testosterone (Linguets) for impotence. The patient claims that this therapy helped his feeling of nervousness, but he remained impotent and periodic hypertension, with blood pressure as high as 250 mm. Hg, was recorded.

In addition to the symptoms mentioned above, the patient on occasion noted flickering spots before his eyes, dyspnea, precordial pain, marked salivation followed by marked thirst, and syncope, which occurred at least 10 times. The number of attacks increased in frequency and severity just prior to admission; consequently he sought hospitalization for further diagnosis and treatment.

Physical Examination.—The patient was a well-developed, well-nourished intelligent white man, who talked rapidly and appeared to be nervous and whose face and neck were flushed almost constantly. The blood pressure varied from 130/90 to 160/120, sometimes within a period of two minutes. The pulse rate was 100 per minute, strong and regular. Mild retinal arteriolar narrowing and arteriovenous nicking were seen on funduscopic examination. Auscultation of the heart disclosed no abnormalities. Results of the remainder of the examination were essentially normal.

Laboratory Findings.—The hemoglobin, erythrocyte count, leucocyte count, and differential cell count were all within normal limits. The sedimentation rate was 15 mm. per hour (Wintrobe); the urea clearance was 90% of normal. The Fishberg concentration and dilution test was also normal. The remainder of the laboratory examinations, including determinations of blood urea nitrogen, blood glucose, intravenous and oral glucose tolerance, 17-ketosteroids level and Thorn test, are recorded in the Table.

4. (*a*) de Vries, A.; Rachmilewitz, M., and Schumert, M.: Pheochromocytoma with Diabetes and Hypertension: Report of 2 Cases Cured by Operation, Am. J. Med. **6**:51, 1949. (*b*) McCullagh, E. P., and Engel, W. J.: Pheochromocytoma with Hypermetabolism, Ann. Surg. **116**:61, 1942.

5. (*a*) Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in Blood Preoperatively During Hypertensive Crises, Ann. Surg. **106**:85, 1937. (*b*) Espersen, T., and Dahl-Iversen, E.: Clinical Picture and Treatment of Pheochromocytoma of Suprarenal: Two Own Cases, One with Paroxysmal Hypertension Improved by Treatment with Methylthiouracil and Cured by Surgical Intervention, Acta chir. scandinav. **94**:271, 1946. (*c*) Calkins, E., and Howard, J. E.: Bilateral Familial Pheochromocytoma with Paroxysmal Hypertension: Successful Surgical Removal of Tumors in 2 Cases, with Discussion of Certain Diagnostic Procedures and Physiological Considerations, J. Clin. Endocrinol. **7**:475, 1947.

6. Mortell, E. J., and Whittle, J. P.: Pheochromocytoma: A Case Report with Certain Observations on the Pathologic Physiology, J. Clin. Endocrinol. **5**:396, 1945.

The electrocardiogram was compatible with early left ventricular hypertrophy, and the ballistocardiogram was nonspecifically abnormal.

The 24-hour uptake of 160 μ of radioactive I^{131} was 14.3%.

Roentgenograms of the chest, skull, and abdomen were normal.

Course in the Hospital and Special Procedures.—Daily fluctuations of the patient's blood pressure ranged from 120/80 to 260/200, and he suffered from 3 to 15 of the above described attacks per day. Symptoms varied from only profuse sweating to episodes of severe headaches, precordial pain, dyspnea, and a sense of impending fainting. Forced hyperventilation also produced such an attack. A cold pressor test caused the systolic and diastolic pressures to rise 30 mm. After sleep induced by 9 grains (540 mg.) of amobarbital sodium (Amytal sodium) the diastolic pressure failed to fall below 100 mm. Following the intravenous administration of

Laboratory Findings Before and After Surgery in a Patient with Pheochromocytoma

	Before Surgery	After Surgery
Urinalysis		
Specific gravity	1.020	1.013
Albumin	1+	Negative
Microscopic examination	15-20 hyaline casts/high power field	Normal
Blood sugar, mg./100 cc.*	154-164	82-84
Glucose tolerance (oral), mg./100 cc.		
Fasting	154	82
30 min.	210	113
60 min.	232	74
120 min.	72	72
180 min.	92	76
Glucose tolerance (I. V.), mg./100 cc.		
Fasting	142	101
30 min.	236	134
45 min.	197	107
60 min.	194	104
90 min.	158	95
Blood urea nitrogen, mg./100 cc.	16	17
Basal metabolic rate	+19 and +20%	+8, +0, −11%
24-hr. urinary 17-ketosteroids, mg.†	15	9-13
Uropepsin excretion, units/hr.‡	75.8-77.5	12.2-69
Eosinophile studies		
0.3 mg. epinephrine subcutan.		
Fasting	231	638
4 hr.	264	638
25 mg. corticotropin		
Fasting	210	770
4 hr.	262	682
Electrocardiogram, height of R in Lead V_6 + S in VI, mm.	73	37

* Folin-Wu method (normal, 80 to 120 mg. per 100 cc.).
† Zimmerman method (normal for males, 10 to 22 mg. per 24 hours).
‡ Normal, 15 to 40 units per hour.

0.015 mg. of histamine base the patient became tense and pale and complained of headache, particularly in the retro-orbital areas; precordial pain; dyspnea, and a feeling of light-headedness. At this time the blood pressure rapidly rose to over 300 mm. and started down after one and a half minutes. As the blood pressure declined, the patient flushed generally, salivated profusely, and stated that he felt relieved of his headache and the other symptoms (Fig. 1). Other pharmacologic tests added further proof to the diagnosis (Figs. 2, 6, 7, and 8). It is interesting to note that piperoxan (Benodaine) caused little fall in the blood pressure when the blood pressure was slightly elevated but it partially blocked the pressor response of intravenously administered histamine. It should be pointed out that after the injection of the standard dose of piperoxan hydrochloride (2 mg. per kilogram of body weight) the patient had no spontaneous attacks for a period of hours. Phentolamine (Regitine) administered intramuscularly failed to lower the blood pressure (Fig. 2).[7]

7. Our experimental supply of phentolamine (Regitine), which was over two years old, was sent back to the Ciba Laboratory, where tests showed that it had lost its potency.

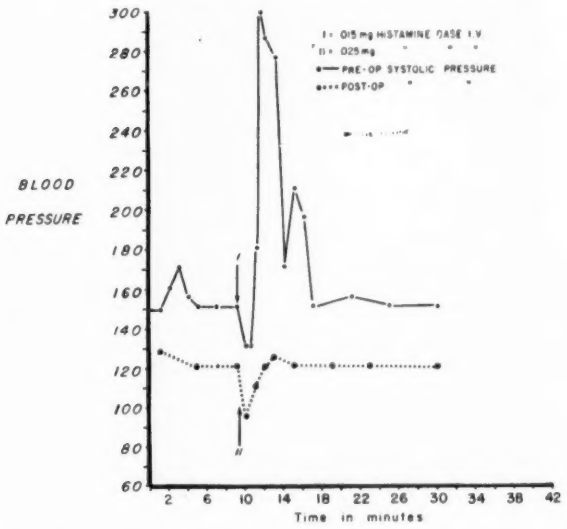

Fig. 1.—Blood pressure responses to the intravenous administration of histamine base before and after surgery.

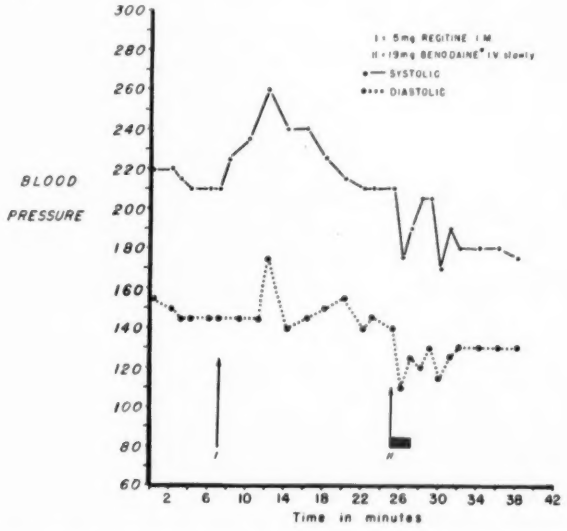

Fig. 2.—Pharmacologic responses to the adrenolytic and sympatholytic agents phentolamine (Regitine) and piperoxan (Benodaine), as measured by the blood pressure. Both responses are considered negative in a case of pheochromocytoma.

Fig. 3.—Roentgenogram of abdomen taken during retroperitoneal oxygen insufflation with simultaneous aortography. The tumor, surrounded partially by air, is clearly seen at the superior pole of the right kidney.

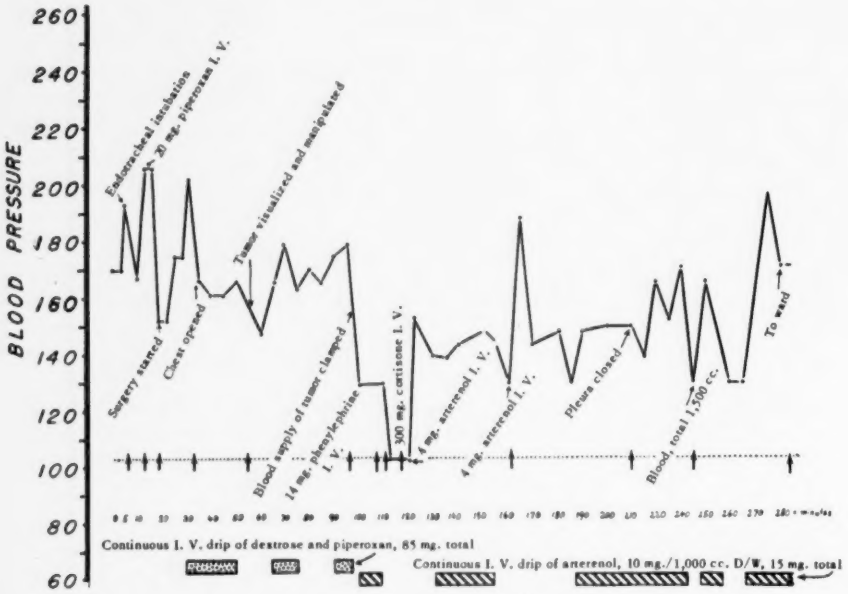

Fig. 4.—Systolic blood pressure recorded throughout operative procedure.

Oxygen, 1,000 cc., was injected retroperitoneally, and the abdomen was studied by intravenous pyelography, planography, and aortic arteriography. In each case, a 6 by 6 cm. mass was visualized above the superior pole of the right kidney (Fig. 3). Planography revealed the tumor mass to be about 8 cm. from the posterior body wall.

Three days prior to surgery, the patient was given 25 mg. of testosterone propionate intramuscularly daily, with no dimunition in the number or severity of the attacks.

Surgery was performed 20 days after admission. An orange-sized tumor was found lying just superior to the right kidney. During the induction of anesthesia and the initial surgical procedure the blood pressure tended to vary considerably (Fig. 4). Control was attempted by using an intravenous solution of 5% dextrose containing 1 mg. of piperoxan hydrochloride per cubic

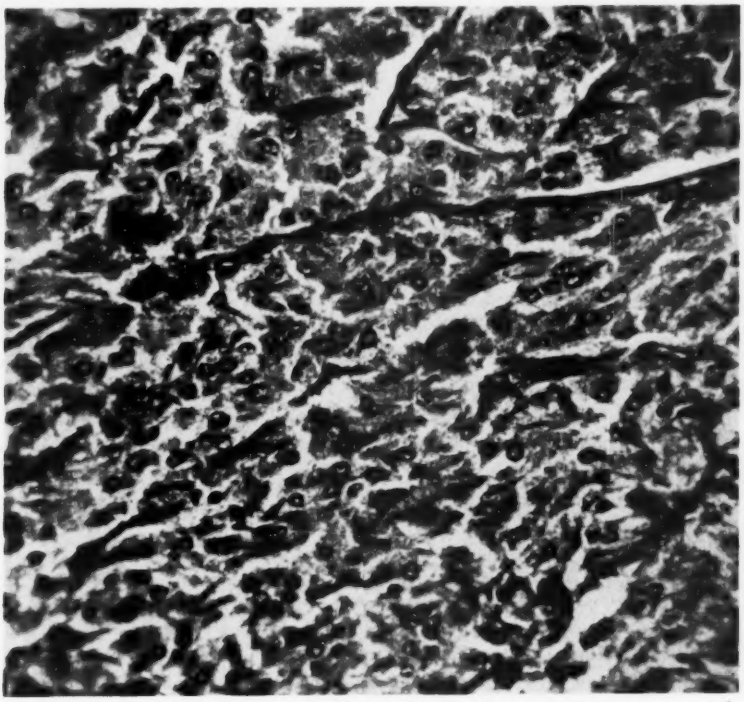

Fig. 5.—Microscopic picture of tumor (× 300), showing solid nests of polygonal and fairly large oval cells having fairly prominent oval nuclei. The cytoplasm of the cells is abundant, finely granular, and pink. Chromaffin stain showed moderate amounts of pigment in certain cells. No malignant cells were seen.

centimeter. During the manipulation of the tumor the blood pressure remained relatively stable. Before the blood supply of the tumor was completely ligated a total of 85 mg. of piperoxan hydrochloride was used.

Just before the last adrenal veins were clamped, a tear in the inferior vena cava caused considerable blood loss and a fall in blood pressure, to 50/40. Immediately after the tumor pedicle was clamped the blood pressure became unobtainable. Intravenous drip of 20 mg. of levarterenol (Levophed) bitartrate per 1,000 cc. of 5% dextrose, 14 mg. of phenylephrine (Neo-Synephrine) hydrochloride, 300 mg. of corticotropin (Cortisone), and whole blood given over a 10-minute period had no effect. At this time, 4 mg. of arterenol given intravenously brought the blood pressure back to normal level. Thereafter the blood pressure varied directly with the rate of flow of the intravenous dextrose solution containing arterenol and epinephrine. The patient was

given corticotropin for several days postoperatively. The blood pressure could not be maintained without this continuous intravenous infusion until the third postoperative day, after 150 mg. of pressor substance had been used.

The postoperative course was uneventful, and the patient felt well. The blood pressure remained around 120/80. All previously described symptoms, including the impotence, disappeared. Postoperative pharmacologic tests were now negative for a pheochromocytoma (see the Table and Figs. 1, 2, 6, 7, and 8). The 24-hour uptake of 160 μc. of radioactive I^{131} was 14.8%.

Pathology.—The excised tumor weighed 120 gm. and measured 8 by 8 by 7 cm. It was well encapsulated and contained a small compressed portion of adrenal cortex over one area. The cut surface had a hemorrhagic yellowish appearance which was compatible with that previously described for similar tumors. Microscopic sections showed the typical chromaffin cells, which appeared benign but which were surrounded with large amounts of hemorrhage (Fig. 5).

Special chemical analyses were performed and revealed that each gram of tumor tissue contained 2.84 mg. of epinephrine and 3.03 mg. of arterenol.[8] The colorimetric method of von Euler [9] was used. Other tests were performed and will be reported separately.

COMMENT

Frankel,[10] in 1886, was the first to find a case of pheochromocytoma. However, it was not until 1926 that the first antemortem diagnosis was made.[1c] In 1937 an increased amount of epinephrine in the blood stream was correlated with the presence of a tumor,[5a] and much later, in 1949, arterenol (norepinephrine, noradrenaline) was also found to be an active pressor substance.[11] The signs and symptoms of pheochromocytoma were first described in 1922, by Labbé and co-workers,[12] and recently Aranow [1c] has completely reviewed the entire subject of pheochromocytoma.

Clinically, this patient presented signs and symptoms compatible with a combination of both the hypermetabolic and the adrenal-sympathetic [13] syndromes of this tumor. These often make a differential diagnosis between a pheochromocytoma and thyrotoxicosis, neurocirculatory asthenia, diencephalic hypertension,[14] and anxiety neurosis [15] difficult. Laboratory findings and pharmacologic tests are then of the utmost importance in establishing the diagnosis.

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8. Analyses were done by Dr. Robert S. Pogrund and staff of the Research Service of the Sawtelle Veterans Administration Hospital, Los Angeles.

9. von Euler, U. S., and Hamberg, U.: Colorimetric Determination of Noradrenaline and Adrenaline, Acta. physiol. scandinav. **19**:74, 1949.

10. Fraenkel, F.: Ein Fall von doppelsteitigem völlig latent verlaufenem Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis, Virchows Arch. Path. Anat. **103**:244, 1886.

11. Holton, P.: Noradrenaline in Tumors of Adrenal Medulla, J. Physiol. **108**:525, 1949. Goldenberg, M.; Faber, M.; Alston, E. J., and Chargaff, E. C.: Evidence for the Occurrence of Nor-Epinephrine in the Adrenal Medulla, Science **109**:534, 1949.

12. Labbé, M.; Tinel, J., and Doumer: Crises solaires et hypertension paroxystique en rapport avec une tumeur surrénale, Bull. et mém. Soc. méd. hôp. Paris **46**:982, 1922.

13. Goldenberg, M.: Adrenal Medullary Function, Am. J. Med. **10**:627, 1951.

14. Page, I. H., and Corcoran, A. C.: Arterial Hypertension, Chicago, Year Book Publishers, Inc., 1949, p. 64.

15. Crede, R. H., and Kerr, W. J.: Pheochromocytoma: Report of a Case Simulating Acute Anxiety Attacks, Postgrad. Med. **11**:288, 1952.

Pharmacologic Tests.—Roth and Kvale,[16] in 1945, first used intravenous histamine as a diagnostic test. In this patient, little doubt existed as to the diagnosis after such a definite positive reaction (Fig. 1). However, false negative[1d,f] and false positive reactions[17] have been reported. No serious side reactions have been reported. However, particularly in the aged, one should be prepared to bring the pressure down immediately when there is a prolonged or severe reaction, by using rapidly acting adrenolytic and sympatholytic drugs, e. g., piperoxan and phentolamine. The pressor effect of histamine was somewhat blocked but not abolished by intravenous piperoxan (Fig. 6).

La Due, Murison, and Pack[18] first obtained a histamine-like response in a patient with pheochromocytoma with 400 mg. of tetraethylammonium bromide

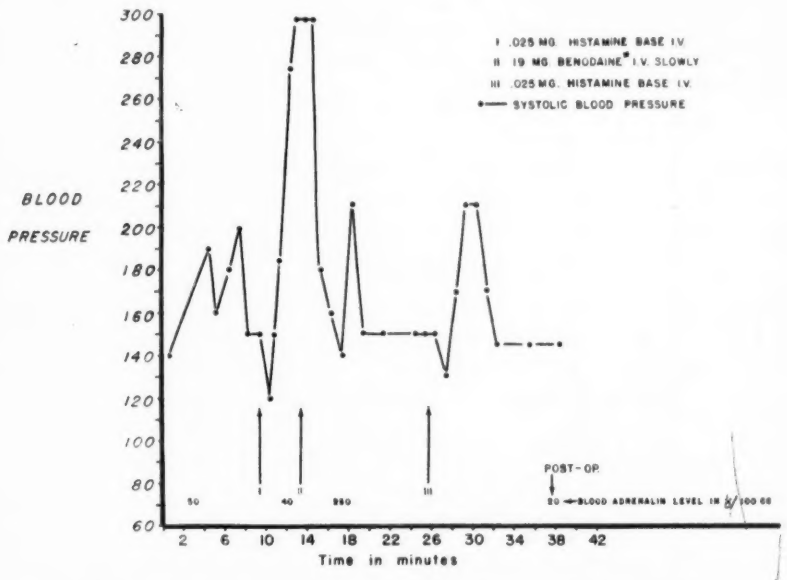

Fig. 6.—Blood pressure responses to the use of histamine and piperoxan intravenously. Blood epinephrine (Adrenalin) levels were determined during the attack and postoperatively. See text for details.

given intravenously, and subsequent confirmation has been plentiful.[19] In this patient, a dose of 150 mg. on two occasions produced positive tests prior to surgery, without side effects. This smaller dose is therefore recommended (Fig. 7).

16. Roth, G. M., and Kvale, W. F.: A Tentative Test for Pheochromocytoma, Am. J. M. Sc. **210**:653, 1945.

17. Footnote 1*d*, *e*, and *f*.

18. La Due, J. S.; Murison, P. J., and Pack, G. T.: The Use of Tetraethylammonium Bromide as a Diagnostic Test for Pheochromocytoma, Ann. Int. Med. **29**:914, 1948.

19. (*a*) Gould, J., and Mundal, A. L.: Multifocal Ventricular Tachycardia Induced by Etamon in a Case of Pheochromocytoma, Am. Heart J. **42**:460, 1951. (*b*) Anderson, W. H.; Rolufs, L. S., and Doerner, A. A.: The Use of Pharmacological Tests in the Diagnosis of Pheochromocytoma, ibid. **43**:252, 1952. (*c*) Footnote 1*d*, *e*, and *g*.

Since piperoxan was first used in 1947 as a diagnostic test in pheochromocytoma,[20] the literature has many reports regarding it.[19b] False positive reactions have been noted with frequency in uremia.[21] Grimson has suggested that this is due to the small amounts of epinephrine circulating in the blood in this condition.[21b] As in this case, false negative reactions are fairly common.[22] Although the amount of drug injected did not appreciably lower the blood pressure (Fig. 2), the patient was relieved of minor attacks for as long as five hours after the test. Our experience agrees with that of Calkins and his associates,[23] who state that the degree of inhibition of epinephrine by piperoxan is proportional to the amounts used and can be altered by increasing the concentrations. This patient preoperatively had 2½ times the normal amount of epinephrine circulating in his blood stream, and during the height of the attack 12½ times the normal amount was found. This may explain

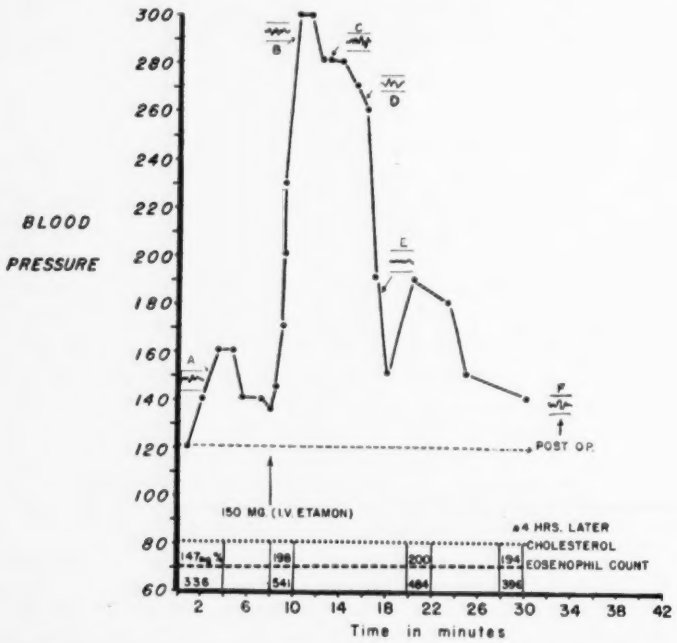

Fig. 7.—Intravenous administration of 150 mg. tetraethylammonium (Etamon) chloride. Systolic blood pressure response, serum cholesterol, and total eosinophile count are recorded. Sketched-in figures on graph represent ballistocardiograph readings, which were nonspecifically abnormal before and during the test and normal after surgery.

20. Goldenberg, M.; Snyder, C. H., and Aranow, H., Jr.: New Test for Hypertension Due to Circulating Epinephrine, J. A. M. A. **135**:971, 1947.

21. (*a*) Taliaferro, I.; Adams, R. A., and Haag, H. B.: Benzodioxan Test: Fall in Blood Pressure Following Its Use in a Case of Renal Hypertension, J. A. M. A. **140**:1271, 1949. (*b*) Grimson, K. S.: Diagnostic Procedures in the Selection of Patients for Definitive Treatment of Arterial Hypertension, read before the Los Angeles County Heart Symposium, October, 1952.

22. Footnote 1*d* and *f*. Anderson, Rolufs, and Doerner.[19b]

23. Drill, V. A.: Reactions from the Use of Benzodioxane (933 F) in the Diagnosis of Pheochromocytoma, New England J. Med. **241**:777, 1949.

why, as shown in Fig. 6, the piperoxan only partially blocked the pressor response to intravenous histamine and also why so much piperoxan had to be used during surgery (Fig. 4) in order to control the blood pressure level prior to removal of the tumor. Finally, it should be kept in mind that piperoxan has been noted to have serious pressor reactions [24] and in one case precipitated a hypertensive encephalopathy.[25]

Phentolamine was first used and described by Grimson [25] as a diagnostic test and as a therapeutic agent in combating the pressor reactions during surgery for a pheochromocytoma. Iseri and co-workers [26] confirmed Grimson's work. At the present time, because of its rapid and short action and infrequent side reactions, this drug is being used widely instead of piperoxan diagnostically and during surgery for pheochromocytoma. Phentolamine failed in this case. This was attributed to the fact that, after long storage, the drug had lost its potency. Prior to its use in this case, however, this experimental supply of the drug had been used successfully during surgery to prevent abnormal pressor responses in an unreported case.

Resistance to parenterally administered epinephrine has been previously noted.[6] Mayock and Rose [27] had a patient who did not respond to 2 cc. of 1 : 1,000 epinephrine solution administered subcutaneously. Shapiro [16] showed that in a group of normal and hypertensive persons there was a physiologic response after the intravenous administration of 0.25 cc. and 0.50 cc. of 1 : 10,000 epinephrine solutions. In agreement with the findings in their patient who had a pheochromocytoma, it was found in this case that there was no response, preoperatively, until 1.5 cc. of 1 : 10,000 epinephrine solution was used. Following surgery sensitivity to epinephrine increased (Fig. 8). Our case also bears out previous experience that when there is an increased tolerance to exogenous epinephrine there will also be a need for large amounts postoperatively to maintain the blood pressure.[16] If this experience proves to be constant, the response to exogenous epinephrine may be used to predict the postoperative course.

Roentgenographic Diagnosis.—Rivas [28] and Steinbach [29] reported the use of retroperitoneal injection of oxygen for the diagnosis of abdominal masses by air contrast. This procedure is safe and is not attended by air embolism or false positive and false negative results that one sees with perirenal air insufflation.[30] Because of the simplicity of this maneuver, it was performed on this patient three times, with-

24. Koonce, D. H.; Pollock, B. E., and Glassy, F. J.: Bilateral Pheochromocytoma Associated with Neurofibromatosis: Death Following Aortography, Am. Heart J. **44**:901, 1952. Drill.[23]

25. Grimson, K. S.; Longino, F. H.; Kernodle, C. E., and O'Rear, H. B.: Treatment of a Patient with a Pheochromocytoma: Use of an Adrenolytic Drug Before and During Operation, J. A. M. A. **140**:1273, 1949.

26. Iseri, L. T.; Henderson, H. W., and Deer, J. W.: Use of Adrenolytic Drug, Regitine, in Pheochromocytoma, Am. Heart J. **42**:129, 1951.

27. Mayock, R. L., and Rose, E.: Insensitivity to Epinephrine in a Patient with a Functioning Tumor of the Adrenal Medulla, Am. J. M. Sc. **213**:324, 1947.

28. Rivas, R. M.: Roentgenological Diagnosis: Generalized Subserous Emphysema Through a Single Puncture, Am. J. Roentgenol. **64**:723, 1950.

29. Steinbach, H. L.; Lyon, R. P.; Miller, E. R., and Smith, D. R.: Extraperitoneal Pneumography: A Preliminary Report, California Med. **75**:202, 1951.

30. Smithwick, R. H.; Greer, W. E. R.; Robertson, C. W., and Wilkins, R. W.: Pheochromocytoma: A Discussion of Symptoms, Signs and Procedures of Diagnostic Value, New England J. Med. **242**:252, 1950.

out sequelae. A coned down view of the adrenal area is superior to the routine abdominal supine film.[31] Intravenous pyelography, planography, and arteriography may be done in conjunction with the oxygen insufflation.

Endocrinologic Aspects.—Some authors [1g] have felt that there should be some degree of adrenal cortex insufficiency in cases of pheochromocytoma, because of the effects of epinephrine on the adrenal-pituitary axis and also because of local compression of one or both adrenals by the tumor.[32]

From experimental work Raab [33] and Long [3b] demonstrated that the action of epinephrine on the hypothalamic-hypophyseal system results in release of corticotropin (adrenocorticotropic hormone, ACTH). They present evidence that the chronic use of parenteral epinephrine will lead to adrenal insufficiency. Sayers,[3d] in an excellent review, summarized the various theories on the site of action of epineph-

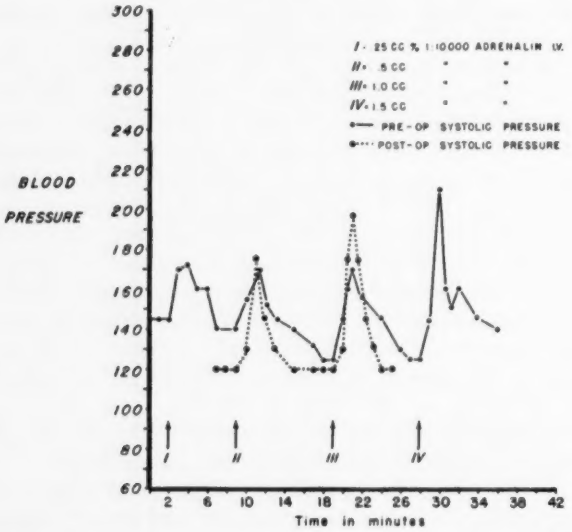

Fig. 8.—Blood pressure responses before and after surgery to the intravenous administration of varying doses of 1 : 10,000 solution of epinephrine.

rine. He concluded that, "discharge of epinephrine contributes to the increase in the adrenocorticotropic activity of the adenohypophysis in numerous acute stresses." However, the question of "whether the action of epinephrine is a necessary and essential link in the series of events which lead to increased secretion of cortical hormone during stress or whether epinephrine acts like other nonspecific stresses to increase the needs of the tissues for cortical hormone" is not yet settled. He does state that large toxic doses of epinephrine, like any other toxic substance, will have a nonspecific effect causing the pituitary to release corticotropin.

31. Pennes, A. E.: Personal communication to the author.

32. Matisseck, H.: Das Phäochromocytoma und seine Beziehungen zur Nebennierenrindenfunktion, Langenbecks Arch. klin. Chir. **365**:517, 1950.

33. Raab, W.: Pathogenic Patterns of Essential Hypertension, Exper. Med. & Surg. **6**:464, 1948.

Increased blood levels of circulating epinephrine and arterenol have been demonstrated in cases of pheochromocytoma. This is probably responsible for the increased amounts found excreted in the urine.[34] In this case, using the Shaw-Whitehorn method,[35] there was found before surgery two and a half times the amount of circulating epinephrine found after surgery. During an attack induced by the intravenous administration of histamine the blood epinephrine level rose to 12½ times the postoperative value, of 20 γ per 100 cc. (Fig. 6). This rise occurred despite evidence previously noted of increased resistance to exogenous epinephrine. Therefore, if there is an intact adrenal-pituitary axis present, one would expect to find changes that would support some of the theories listed above.

The lack of an eosinopenic response to the usual subcutaneous administration of epinephrine and to the intramuscular administration of 25 mg. of corticotropin might lead one to suspect the integrity of the adrenal-pituitary axis in this case. The normal preoperative 24-hour urinary excretion of 17-ketosteroids, however, would be against this. Further, these same negative responses occurred postoperatively, but the intravenous administration of 5 mg. of corticotropin over an eight-hour period produced a normal eosinopenic response. I conclude that there was a normal adrenal-pituitary axis and that the lack of response to epinephrine and later to intramuscular administration of corticotropin was an indication of resistance to exogenous epinephrine and an increased enzymatic destruction of corticotropin in the muscular tissue, respectively.

A review of the literature of cases of pheochromocytoma [36] reveals the 17-ketosteroid urinary excretion to vary from 1 mg. to 11.8 mg. per 24 hours, with an average of 9 mg. per 24 hours. Taking into consideration the various chemical techniques used, the average result may be interpreted to fall in the low-normal range.

In this case, the 24-hour urinary excretion of 17-ketosteroids was normal. The urinary uropepsin levels (Table) were elevated, except for a short time immediately following surgery. This finding, of elevated urinary uropepsins, cannot be interpreted to mean adrenal cortex hyperactivity, since a fall did not occur in the convalescent postoperative period.

For the reasons mentioned earlier, Shapiro,[1g] finding the 24-hour urinary excretion of 17-ketosteroid to be 1 mg. in a case of pheochromocytoma, suggested that this resulted from adrenal insufficiency. Sprague,[36a] on the other hand, found an

34. von Euler, U. S.: Increased Urinary Excretion of Noradrenaline and Adrenaline in Cases of Pheochromocytoma, Ann. Surg. **134**:929, 1951.

35. Normal values are 14 to 22 γ per 100 cc. This method is only relatively accurate, owing to nonspecific chemical methods used. Analyses gave only an estimate of the relative magnitude of the catechol amines present. However, the differences are quite clear. J. R. Goodman, Ph.D., performed the analyses.

36. (*a*) Calkins, E.; Dana, G. W.; Seed, J. C., and Howard, J. E.: On Piperidylmethyl-Benzodioxane (933 F), Hypertension, and Pheochromocytoma, J. Clin. Endocrinol. **10**:1, 1950. (*b*) Koffler, I. A.; Buck, G.; Wingard, C.; Hitchcock, P.; Guthrie, R., and Teague, R. S.: A Case of Pheochromocytoma: Diagnosis by the Benzodioxane Test: Urinary Hormone Studies and Nor-Epinephrine Assay of the Tumor, ibid. **10**:897, 1950. (*c*) Blacklock, J. W. S.; Ferguson, J. W.; Mack, W. S.; Shafar, J., and Symington, T.: Phaeochromocytoma, Brit. J. Surg. **35**:179, 1947. (*d*) Thorn, G. W.; Hindle, J. A., and Sandmeyer, J. A.: Pheochromocytoma of the Adrenal Associated with Persistent Hypertension: Case Report, Ann. Int. Med. **21**:122, 1944. (*e*) Shapiro and others.[1g] (*f*) McCullagh and Engel.[4b] (*g*) Mortell and Whittle.[6] (*h*) Goldenberg.[13] (*i*) Crede and Kerr.[15]

elevated urinary excretion of 17-ketosteroids. This, plus the finding of a delayed return of the blood pressure to normal, led him to suggest that in some cases of pheochromocytoma there was adrenal cortex hyperactivity. Neff and co-workers [37] reported a case of a female infant with all the signs of a Cushing syndrome which disappeared following the surgical removal of a pheochromocytoma.

All the evidence so far leads me to the conclusion that the high blood level of circulating epinephrine in cases of paroxysmal or persistent hypertension due to pheochromocytomas has no long-range effect on the adrenal-pituitary axis.

The carbohydrate and metabolic effects of epinephrine are well known. Arterenol, on the other hand, in the physiologic range, has been found to have few or no such actions.[36h] Cori was the first to show that the amounts of epinephrine necessary to produce these carbohydrate and metabolic effects are considerably smaller than the amounts needed to produce pressor effects.[38] De Vries applied this fact to pheochromocytomas. He felt that though the resting level of epinephrine was not negligible it was sufficient to produce metabolic changes but insufficient to produce pressor effects.[4a] As noted earlier, in this case the epinephrine blood level during an attack was five times greater than the preattack level, which, in turn, was greater than normal. Therefore the signs and symptoms of hyperthyroidism and diabetes mellitus can readily be explained in the absence of continuous hypertension. The clinical findings of an elevated basal metabolic rate and an abnormal glucose tolerance have been well described.[39]

Medical and surgical therapy for thyrotoxicosis has been undertaken in cases of pheochromocytoma on numerous occasions before the correct diagnosis was established.[40] Rabb thought that epinephrine stimulates the thyroid gland directly or via the pituitary to secrete more thyroxin and also that thyroxin potentiates the normal and toxic effects of epinephrine.[41] The finding in this case of a normal 24-hour uptake of radioactive iodine (I^{131}) does not support the first part of the preceding concept. More likely, the occasional finding of an enlarged thyroid gland may be attributed to changes in the vasomotor tonus of the thyroid vessels.[42] The elevated basal metabolic rate is a reflection of the increased tissue consumption of oxygen, which is a pharmacologic response to epinephrine.[36h]

Throughout the literature one finds cases reported in which the carbohydrate metabolism is so deranged that patients present themselves with the typical signs and symptoms of diabetes mellitus, when they have pheochromocytomas.[43] These

37. Neff, F. C.; Tice, C. M.; Walker, G. A., and Ocherblad, N.: Adrenal Tumor in Female Infant with Hypertrichosis, Hypertension, Overdevelopment of External Genitalia, Obesity, but Absence of Breast Enlargement, J. Clin. Endocrinol. **2**:125, 1942.

38. Cori, C. F., and Buchwald, K. W.: Effect of Continuous Intravenous Injection of Epinephrine on Carbohydrate Metabolism, Basal Metabolism and Vascular System of Normal Men, Am. J. Physiol. **95**:71, 1930.

39. Footnote 1*b* and *c*. Smithwick and others.[20]

40. Footnote 5. McCullagh and Engel.[4b]

41. Raab, W.: Adreno-Sympathetic Heart Disease (Neurohormonal Factors in Pathogenesis and Treatment), Ann. Int. Med. **28**:1010, 1948.

42. Bauer, J., and Belt, E.: Paroxysmal Hypertension with Concomitant Swelling of the Thyroid Due to Pheochromocytoma of Right Adrenal Gland: Cure by Surgical Removal of Pheochromocytoma, J. Clin. Endocrinol. **7**:30, 1947. Rein, H.; Liebermeister, K., and Schneider, D.: Schilddrüse und Carotissinus als funktionelle Einheit, Klin. Wchnschr. **11**:1636, 1932.

43. (*a*) Duncan, L. E., Jr.; Semans, J. H., and Howard, J. E.: Adrenal Medullary Tumor (Pheochromocytoma) and Diabetes Mellitus: Disappearance of Diabetes After Removal of the Tumor, Ann. Int. Med. **20**:815, 1944. (*b*) Footnote 4.

cases run courses similar to that of diabetes, and the patients are treated with insulin with varying responses. In about 60% of the reviewed cases of pheochromocytoma there is a fasting blood sugar level of over 120 mg. per 100 cc. In 25 to 40% the glucose tolerance curve is typically diabetic. There is no relationship between the degree of hypertension and the level of hyperglycemia, but the highest blood glucose levels are found during the paroxyms of hypertension.[43a] This type of "diabetes" is physiologically attributable to the chronic epinephremia seen with a pheochromocytoma.[44] The hyperglycemia observed is due to the glycolytic effect of epinephrine on the liver. Although epinephrine diabetes and diabetes mellitus are very similar, differences exist. For example, acidosis occurring in cases of pheochromocytoma does not create a decrease in the liver glycogen. Unlike the condition in true diabetic acidosis, the liver glycogen is normal or slightly elevated in amount.[45] This is due to the action of epinephrine on the muscle glycogen, which is broken down, depleted, and the breakdown products taken to the liver for resynthesis into glycogen.[45a] The ketosis seen in cases of pheochromocytoma is a result of the accelerated fat catabolism caused by the direct action of epinephrine.[43a]

Most of the manifestations of diabetes disappear following surgery.[46] There are a few cases in which diabetes persists.[47] In animals continuous intravenous administration of epinephrine fails to produce persistent diabetes.[43a] Thorn reported a case in which there was persistent hypertension for seven years due to a pheochromocytoma, without detectable derangement of carbohydrate metabolism, and, as a matter of fact, the patient had a flat glucose tolerance curve.[36d] Hyperglycemia, clinically, is not as constant a finding as paroxysmal hypertension in pheochromocytoma. To summarize, the amounts of circulating epinephrine needed to produce these various responses vary greatly and are inconstant; therefore other unknown mechanisms must play a role. This indicates the need for further study.

SUMMARY

A case of pheochromocytoma studied before and after surgery is reported. Special attention is given to the laboratory findings, pharmacologic tests, and roentgenographic diagnostic procedures.

The literature on pheochromocytomas is reviewed regarding the effect of epinephrine on the adrenal-pituitary axis. This review and the findings in this case lead me to conclude that chronic epinephremia does not produce adrenal cortex changes.

The metabolic effects of epinephrine are discussed. The clinical pictures of thyrotoxicosis and diabetes in cases of pheochromocytoma are noted.

The relationship of these symptoms and findings to pheochromocytoma are analyzed.

43 Southridge Rd.

44. de Vries, Rachmilewitz, and Schumert.[43a] Goldenberg.[13]

45. (*a*) Cori, C. F.: Mammalian Carbohydrate Metabolism, Physiol. Rev. **11**:143, 1931. (*b*) de Vries, Rachmilewitz, and Schumert.[43a]

46. Footnote 1*b* and *c*. de Vries, Rachmilewitz, and Schumert.[43a] Duncan, Semans, and Howard.[43a]

47. McCullagh and Engel.[43b] Duncan, Semans, and Howard.[43a]

OBSERVATIONS OF GASTRIC MOTILITY DURING GASTRIC CRISIS

S. I. PATRICK, M.D.
AND
R. J. REEVES, M.D.
DURHAM, N. C.

THE PROBLEM of syphilis involving the stomach itself has been well covered in the literature. There is no typical x-ray picture. A gumma in the pyloric region may simulate pyloric stenosis or may appear to be an ulcer or a new growth. An infiltrating lesion of the wall closely resembles and cannot from a single study be separated from an infiltrating tumor. The commonest finding, however, is the hourglass deformity of the stomach.[1]

Visceral attacks occur in 10% of persons suffering from tabes dorsalis. They may constitute an initial symptom and often occur in the preataxic stage; however, they are usually accompanied by pupillary signs or infection in the blood or spinal fluid.

Of the visceral crises the gastric type is commonest. The onset generally is featured by abrupt epigastric pain followed by retching and vomiting. Neither the pain nor the vomiting disappears with these ejections, and they may continue for days with rapid loss of weight and strength followed by sudden cessation. Roentgen examination of the stomach is frequently misinterpreted because of the spasm which is generally present.

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Dr. Patrick is a trainee, United States Public Health Service.

1. (*a*) Berger, H.: A New Diagnostic Criterion for Gastric Syphilis, Gastroenterology **14**:147, 1950. (*b*) Crohn, B. B.: Affections of the Stomach, Philadelphia, W. B. Saunders Company, 1927. (*c*) Eustermann, G. B.: Gastric Syphilis: Observations Based on 93 Cases, J. A. M. A. **96**:173, 1931; (*d*) Syphilis of the Stomach, A. J. Med. Sc. **153**:21, 1917. (*e*) Golob, M.: Gastric Syphilis: Rev. Gastroenterol. **5**:322, 1938. (*f*) Gottlieb, C.; Beranbaum, S. L., and Weiner, M. L.: Syphilis of the Stomach, Radiology **59**:193, 1952. (*g*) Harris, S., Jr., and Youmans, J. B.: Syphilis of the Stomach: Report of 7 Cases, South. M. J. **24**:847, 1931. (*h*) Hill, L. L., Jr.: Syphilis of the Stomach, Am. J. Syph. **14**:199, 1930. (*i*) Laird, S. M.: Organic Gastric Syphilis: Review and Case Report, Lancet **2**: 712, 1938. (*j*) LeWald, L. T.: Roentgen Diagnosis of Gastric Syphilis, J. A. M. A. **96**:179, 1931. (*k*) McPeak, C. N.: Syphilis of the Stomach: With Report of Unusual Case, Am. J. Roentgenol. **43**:832, 1940. (*l*) Moore, A. B., and Aurelieus, J. R.: Roentgenologic Manifestations in 87 Cases of Gastric Syphilis, ibid. **19**:425, 1928. (*m*) O'Leary, P. A.: Gastric Syphilis: Data Accumulated from 89 Cases, Am. J. Surg. **11**:286, 1931. (*n*) Palmer, E. D.: Syphilis of the Stomach and the Stomach in Syphilis: Review of Literature with Particular Reference to Gross Pathology and Gastroscopic Diagnosis, Am. J. Syph. **33**:481, 1949. (*o*) Parsons, P. B.: Gastric Syphilis, Radiology **36**:371, 1941. (*p*) Raffensperger, E. C.; McDonald, R. J., and Houston, R. A.: Early Gastric Syphilis: Report of a Case with Extensive Infiltration, Ann. Int. Med. **37**:172, 1952. (*q*) Spellburg, M. A., and Norfleet, W. J.: Early Gastric Syphilis, Gastroenterology **2**:191, 1944. (*r*) Singer, H. A., and Dyas, F. G.: Syphilis of the Stomach: with Special Reference to Certain Diagnostic Criteria, Arch. Int. Med. **42**:718, 1928. (*s*) Voss, F. H.: Syphilis of the Stomach: A Case Report, Rev. Gastroenterol. **12**:111, 1945. (*t*) Williams, C., and Kimmelstiel, P.: Syphilis of the Stomach, J. A. M. A. **115**:578, 1940.

Episodes occur at intervals. Attempts have been made to distinguish three clinical forms of visceral crisis: (1) vagal or autonomic, i. e., those associated with intense nausea and vomiting and cardiac malfunction or dysphagia and with only inconspicuous soreness of the skin over the abdomen; (2) sympathetic, in which the last-named features predominate, even to the exclusion of vomiting; (3) phrenic, with the associated syndrome of nausea, shoulder pain, and hiccup.[2]

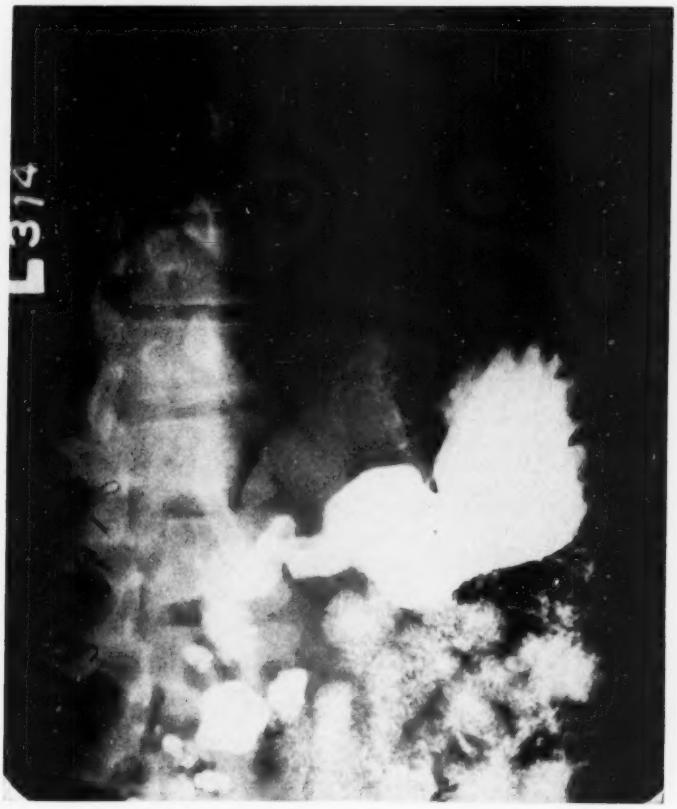

Fig. 1.—Study done in outside hospital two weeks before our examination showing normal peristalsis.

Other visceral crises include intestinal, rectal, and pharyngeal, all of which are less frequent. Laryngeal crises are rare.

We have recently observed a patient during and after an episode of gastric crisis. We found only a sparse amount of information concerning the phenomena which we witnessed and felt that others might benefit from our observations.

Our patient was a 47-year-old Negro man with a 15-year history of attacks of abdominal pain occurring approximately two or three times yearly and lasting for three to four days each

2. (*a*) Bockus, H. L.: Gastro-Enterology, Philadelphia, W. B. Saunders Company, 1943, Vol. I, p. 737. (*b*) Wilson, S. A. K.: Neurology, edited by A. N. Bruce, Baltimore, Williams & Wilkins Company, 1940

time. These episodes were described as being generalized cramping abdominal pain which did not radiate and which required narcotics for relief. During the three years prior to his admission the attacks had been lasting for 8 to 10 days, on each occasion necessitating hospitalization.

The present episode began five weeks prior to his admission to the hospital. The patient had experienced daily pain which required narcotics for relief. He had considerable nausea and vomiting associated with the pain. The vomitus contained bile but no evidence of blood or fecal material. During this five-week period he had lost 50 lb. (22.5 kg.) in weight. Gall bladder and stomach studies made elsewhere and reviewed by us showed no abnormalities (Fig. 1).

Fig. 2.—First study on Oct. 28, 1952, showing fixed lower end of stomach.

The past history revealed that the patient had had "25 arm and hipshots for bad blood." He had been told on one occasion several years prior to admission that his urine was dark and that he was jaundiced.

Physical Examination.—Examination revealed the blood pressure to be 180/100 during an attack and 130/90 at rest. The patient was described as being an acutely ill Negro man who was having intermittent severe cramping abdominal pain. Pertinent physical findings were Argyll Robertson pupils, a normal gait with no changes in position sense in the extremities, diminished vibration sensation over the toes, increased knee jerks, absence of ankle jerks, and normal plantar responses.

Course in the Hospital.—The patient was given several different blocking agents intramuscularly and intravenously without relief of pain. On admission he was placed on a Sippy diet

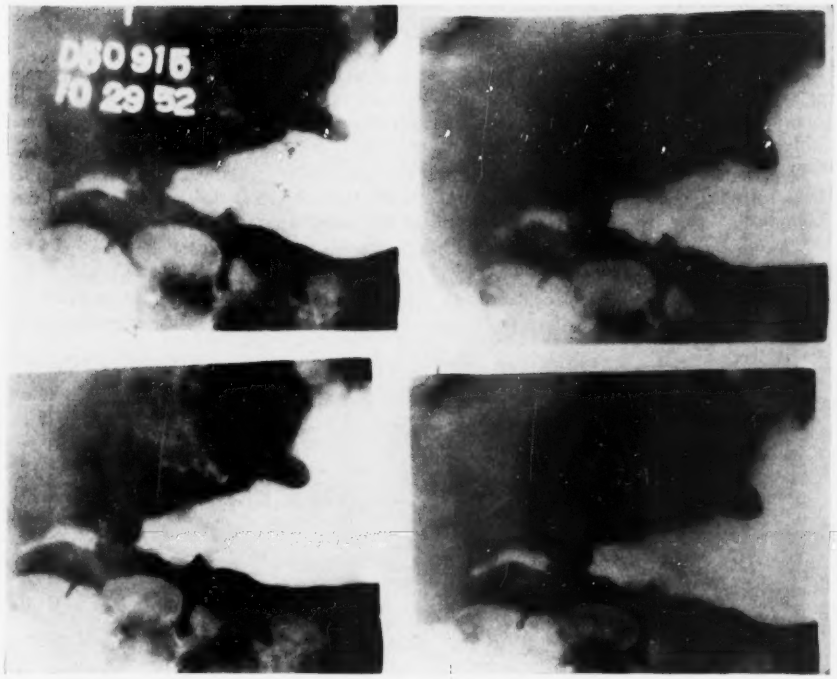

Fig. 3.—Serial films on Oct. 29, 1952, showing absence of peristalsis and only little barium in duodenal bulb. Barium in colon is from previous day.

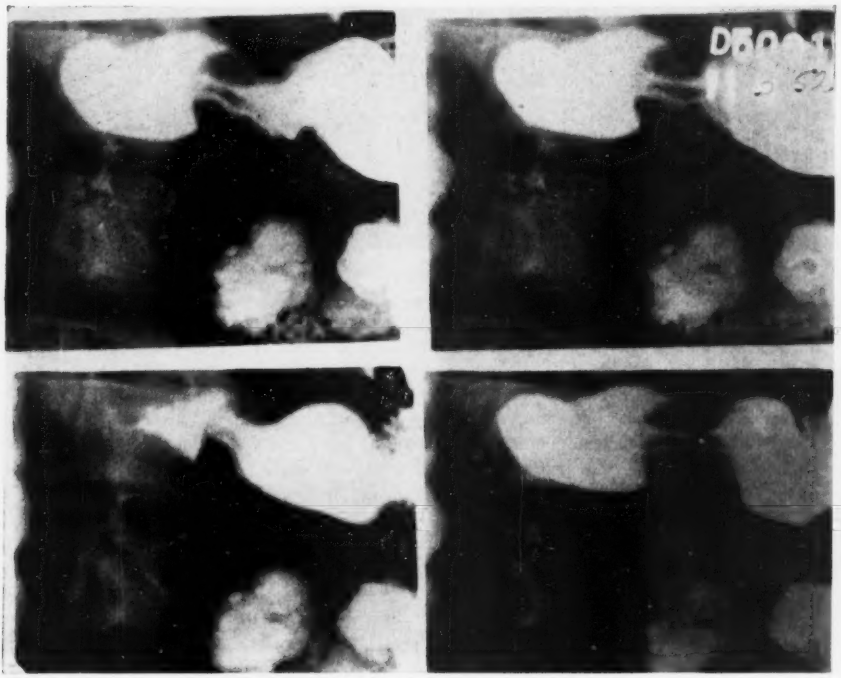

Fig. 4.—Serial study on Nov. 3, 1952, after disappearance of pain, showing normal passage of waves through antrum and good filling of bulb.

without relief of pain and then was transferred to a constant drip of milk, again without relief of pain. The pain was relieved only by narcotics. Roentgen studies made at this time are discussed below. Some five days following admission the pain suddenly ceased and did not recur while he was in the hospital. During this time he received penicillin in massive doses daily.

Laboratory Findings.—The hemoglobin was 11.5 gm., or 74%. The white cell count and differential cell count were normal. The gastric analysis showed zero fasting and 4 degrees of combined acid. The urine was normal. The serological test for syphilis showed a 4+ reaction with a titer of 8. The spinal fluid test for syphilis showed a 4+ reaction with a titer of 16 and a first zone colloidal gold curve. The serum amylase showed 87 units (normal).

Roentgen Findings.—The patient was first seen by one of us (S. P.) on Oct. 28, at which time he was having extreme pain. The preliminary barium, given 6 hours before examination, was

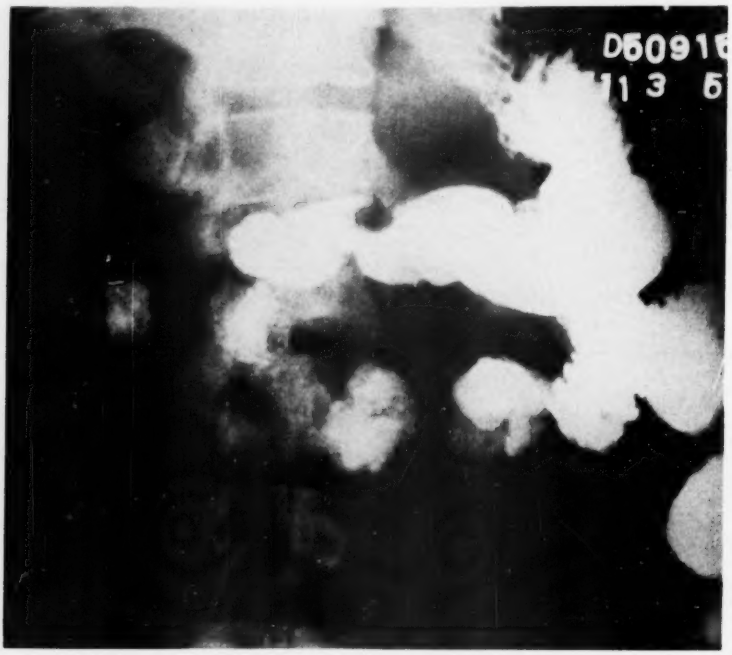

Fig. 5.—Entire stomach on Nov. 3, 1952.

scattered throughout the small bowel. The esophagus showed considerable spasm in the lower third. The stomach was high under the diaphragm, and palpation was unsatisfactory. No peristaltic waves passed through the stomach during a period of one-half hour. The duodenal bulb did not fill. The mucosa of the stomach did not appear unusually abnormal (Fig. 2). The patient was reaxamined the following morning by both of us, and the same stomach findings were present. The duodenal bulb filled partially, and there was a suggestion of an ulcer crater.

It was felt that the patient had an infiltrating lesion of the stomach, probably on an inflammatory basis, although the possibility of a carcinoma or syphilis of the stomach could not be ruled out (Fig. 3).

At this time gastroscopy was done, and the mucosa was described as being normal but no peristaltic activity was present. It was the opinion of the gastroscopist that this represented an infiltrating lesion of the stomach wall.

Three days later, 18 hours after the abrupt disappearance of the abdominal pain, the patient was reexamined by both of us, at which time the esophagus, stomach, and duodenum were normal (Figs. 4 and 5). Such an abrupt change had never before been witnessed by either of us.

Our patient appeared to us on the first and second examinations to have an infiltrating lesion of the stomach and possibly a small ulcer crater. Our third examination revealed a normal stomach. Bockus [2a] mentions briefly that abnormalities in the tone of the stomach occur during a gastric crisis, and he refers to the work of Crohn and Vilensky,[3] who in 1917 made tracings of the peristaltic waves of a patient during a gastric crisis. The tracings, made with a balloon in the stomach, showed marked incoordination of hunger waves of unequal force and height and long periods of atony, all of which were different from the tracings seen in patients suffering from other gastric disturbances.

Fremont-Smith and Ayer [4] in 1925 reported that in 15 of 24 cases of gastric crisis there were abnormal roentgen findings of the stomach. In five of the 15 the abnormalities proved to be of an organic nature, while 10 showed abnormalities due to spasm. X-ray studies of the latter were later repeated or were repeated after the patients had been given atropine, and the organs were found to be normal. Eustermann [5] warns that "one should not be too quick in accepting the roentgen ray diagnosis of a lesion in association with tabes for, as Exner has pointed out, the vagus may undergo degenerative changes in this disease which may in turn bring about spasm defects through faulty innervation."

We believe that the findings in our patient parallel those of the patients reported on by Crohn and Vilensky and Fremont-Smith and Ayer.[6] There was no obstruction in our patient, since he apparently was having peristaltic activity only at varying times up until the time the crisis subsided. This is substantiated by an empty stomach at six hours, with the majority of the barium in the lower small bowel.

From Crohn's book [1b] we find that

> One practically never sees gastric syphilis or in fact visceral syphilis (except cardiovascular) occurring concomitantly with paraluetic manifestations of the disease. That is, in the presence of frank tabes or taboparesis syphilis of the alimentary tract or of the liver may not be expected. Nor for the same reason does one observe tabetic crises and gastric lues occurring in the same patient; the one rules out the presence of the other. This is an important observation since roentgenographic demonstration of an organic defect in a case of tabes or taboparesis is practically always due to the existence of an independent non-specific ulcer or more often a carcinoma ventriculi.

Inasmuch as syphilitic changes are becoming less and less frequent, we feel that these phenomena should be brought to the attention of others.

SUMMARY

A proved case of syphlis in which there was abnormality in the peristaltic activity of the stomach during a gastric crisis, which disappeared after the subsidence of the crisis, is presented.

3. Crohn, B. B., and Vilensky, A. G.: Studies in the Variations of the Tonus of the Gastric Musculature in Health and Disease, Arch. Int. Med. **20**:145, 1917.

4. Fremont-Smith, M., and Ayer, J. B.: The Gastrointestinal Symptoms of Neurosyphilis, J. A. M. A. **85**:1282 1925.

5. Eustermann, G. B., in discussion on Crohn, B. B.: The Existence of Gastric Ulcer with Tabes Dorsalis, J. A. M. A. **77**:2029, 1921.

5. Eustermann, G. B., in discussion on Crohn, B. B.: The Existence of Gastric Ulcer with

Books

Chronic Pulmonary Emphysema, Physiopathology and Treatment. By Maurice S. Segal, M.D., and M. J. Dulfano, M.D. Price, $5.50. Pp. 180, with illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1953.

The fact that this book which deals with only one disease is not at all "padded" shows how internal medicine has grown. The older textbook matters of clinical features, pathology, etc. are thoroughly dealt with, but of especial importance are the chapters on the pathological physiology, the CO_2 intoxication syndrome, and inhalational therapy. Although the specialist in this domain puts on a good show with his therapeutic armamentarium, the fact still remains that obstructive emphysema is a relentlessly progressive disorder and at best the available therapeutic measures ease the inevitable descent. This is an excellent book, however, and highly to be recommended.

Problems of Consciousness: Transactions of the Third Conference, March 10 and 11, 1952. Edited by Harold A. Abramson, M.D. Price, $3.25. Pp. 156, with illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1952.

This volume contains a stimulating but highly semantic discussion of the physiological and psychological aspects of consciousness. The introductory chapter by Kety neatly bridges the impassable gap between consciousness and cerebral metabolism in a manner which sets the spirit of the entire symposium. There follows the usual informal give and take among the participants.

The rest of the book contains an interesting description of hypnotic phenomena by Wolberg and a chapter on experimental work, on sleep and other aspects of brain function, including dreams. This part is ably presented by Monnier. The thesis is supported that "in sleep there is a rerouting of nerve impulses rather than a profound change in energy level."

Diseases of Children. By Sir A. E. Garrod, Frederick E. Batten, Hugh Thursfield, and Donald Paterson. Fifth edition, edited by Alan Moncrieff and Philip Evans. Price, $21.00. Pp. 1,973, in two volumes. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1953.

The scope of this two-volume treatise on pediatrics is extensive. From the tedium of vital statistics one progresses to a most interesting brief on heredity and the causes of congenital malformations. Such basic considerations as acid-base regulation and clinical pathology will be welcomed by the practicing physician.

The thoroughness with which such vital subjects as feeding, growth and development, disorders are discussed render this text adequate for the medical student. The same is also true of infectious diseases. The discussion of treatment, especially as relates to prophylaxis, general nursing, and supportive care is adequate. The use of chemotherapeutic agents and antibiotics is outlined but not adequately discussed. The additions and changes in this field of therapy make such a lack understandable.

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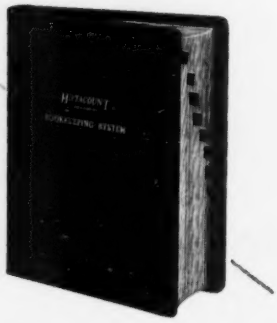

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1. Humphreys, P., et al.: Angiology 3:1 (Feb.) 1952.
2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952.
3. Perlman, A.: Angiology 3:16 (Feb.) 1952.

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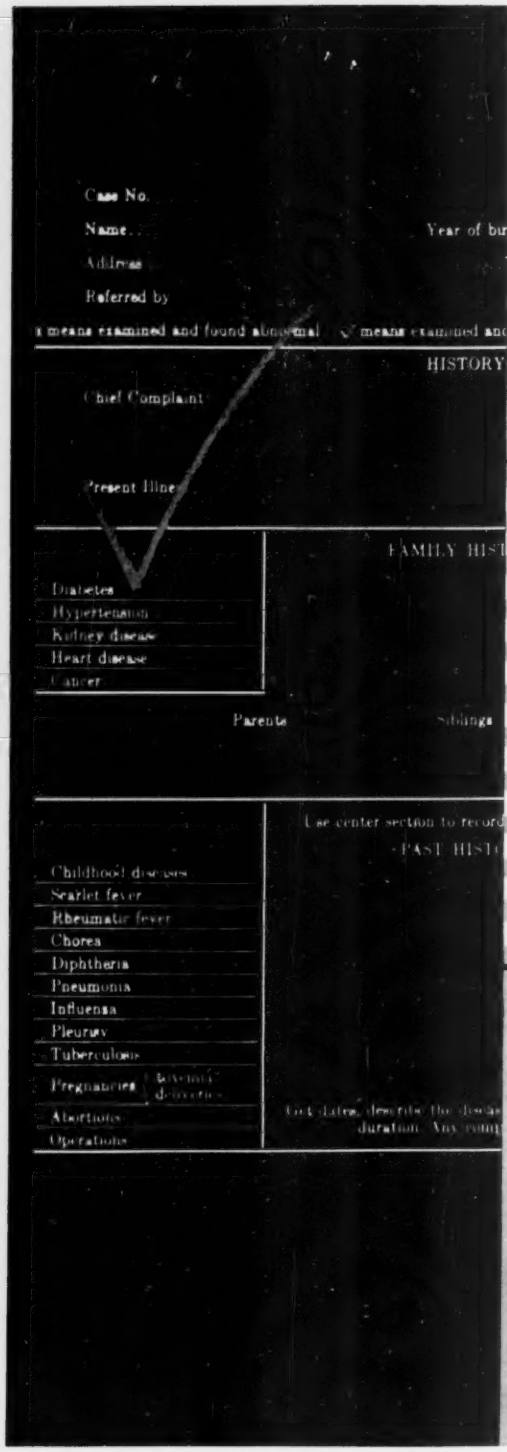

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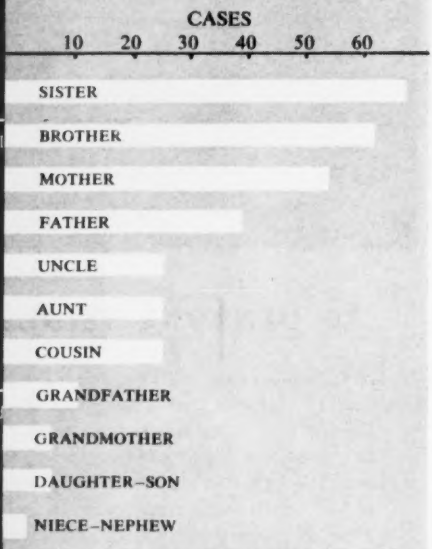

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1. Barach, J. H.: Diabetes and Its Treatment, New York, Oxford University Press, 1949, p. 38.

2. Allen, F. M.: Diabetes Mellitus, in Piersol, G. M., and Bortz, E. L.: Cyclopedia of Medicine, Surgery, Specialties, Philadelphia, F. A. Davis Company, 1951, vol. 4, p. 505.

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